PCT

D INTELLECTUAL PROPERTY ORGANIZATIO
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: CUSHIONING BEADS AND TABLET COMPRISING THE SAME CAPABLE OF FORMING A SUSPENSION

(57) Abstract

Cushioning beads comprising microcrystalline cellulose and a disintegrant (preferably croscarmellose sodium) are disclosed. The cushioning beads are prepared by extrusion-spheronization, followed by freeze-drying. Also disclosed are water-dispersible tablets having high tensile strength, comprising the cushioning beads and biologically active ingredient-loaded beads, wherein optionally, the tablets can contain a viscosity enhancer in the form of separate beads, or as a component of the biologically active ingredient-loaded beads such that viscosity is rapidly generated when the tablets come in contact with water, and a homogeneous suspension is formed, which can be easily swallowed by children and the elderly, with minimal effect on the biologically active ingredient release properties. The tablets are useful for sustained delivery of large doses of biologically active ingredients where swallowing of a large tablet or capsule poses a problem.

CUSHIONING BEADS AND TABLET COMPRISING THE SAME
CAPABLE OF FORMING A SUSPENSION

FIELD OF THE INVENTION

The present invention relates to cushioning beads, and tablets comprising the same, capable of forming a suspension, and useful for delivering biologically active ingredients, such as pharmaceuticals.

BACKGROUND OF THE INVENTION

I.   Introduction

Tablets and capsules are generally unsuitable for administering high doses of biologically active ingredients since individual large dosage forms are difficult to swallow, or necessitate the administration of several tablets or capsules at a time, leading to impaired patient compliance. Further, chewable tablets are not ideal in all situations, especially with older and younger people, due to the need for chewing, the failure to mask unpleasant taste, and their unsuitability for the incorporation of controlled-release coated pellets which can get crushed upon chewing.

Oral liquid suspensions of pharmaceutical materials are designed primarily for those who experience difficulty in swallowing solid medication. However, they are not suitable for the incorporation of controlled-release particles into aqueous vehicles, since this often results in premature release of the biologically active ingredient into the suspending media during storage. This presents a significant challenge, and accounts for the fact that very few sustained-release liquid products are on the market. Different strategies have been investigated to formulate sustained-release suspensions, the most successful utilize ion-exchange resins to bind charged molecules. Limitations of this system include low

- 2 -

drug-loading capability and its applicability to only ionic drugs.

The formulation of a solid oral dosage form, whether tablet or capsule, which disintegrates rapidly in water to form an instantaneous homogenous suspension of adequate viscosity to be swallowed could circumvent the problems of administering large dosages without premature release from controlled-release particles. Moreover, it could provide improved packaging and transportation properties, and a ready measured dose.

The key to the development of such a dosage form is a rapidly disintegrating tablet which disperses to form a viscous suspension. A delay in the development of a viscous gel is essential if disintegration of the tablet is to be achieved. On the other hand, a rapidly developing viscosity is necessary to provide adequate suspension properties.

Conceptually, the system should contain a swellable material which is able to generate viscosity on contact with water, at least one biologically active ingredient for immediate or sustained release delivery of the biologically active ingredient, and a filler system which confers properties, such as compactibility and the capability to disintegrate quickly.

The inclusion of a viscosity increasing agent, as a fine powder, in the tablet matrix without any processing would interfere with disintegration and result in the formation of a voluminous hydrophilic mass which is impossible to disperse. Thus, it is necessary to incorporate such an agent into the tablet as granules or spheres so that the disintegration process occurs before the viscosity build-up.

Beads and coated beads are often incorporated into hard gelatin capsules to provide conventional or controlled release dosage forms, respectively. Compaction of beads into tablets has always been of

5   interest, but during the compaction process there is a possibility that the beads will crack due to the applied force. If the beads have been coated by a rate controlling membrane to sustain or delay the delivery of the biologically active ingredient,

10   cracking of the membrane will cause the delivery system to fail. Matrix fillers involving soft granules or microcrystalline cellulose (MCC) have been used with varying degrees of success.

II.   Sustained Release Liquid Oral
15   Drug Delivery Systems
        Considerable research effort has been spent on oral, solid sustained- or controlled- release drug delivery systems (Ghebre-Sellasie, *Multiparticulate Oral Drug Delivery*, Marcel Dekker, Inc. (1994)).

20   Multi-particulates can be filled into hard gelatin capsules or be compressed into tablets. An alternative approach for the oral administration of multi-particulates is to suspend them in a liquid vehicle to form a suspension or into a dry powder

25   system or a tablet, which is reconstituted with water by the patient prior to administration. These types of dosage forms overcome the above-mentioned problems, and are often preferred for infants, children, and the elderly because of the ease in swallowing and the

30   flexibility in administration.

- 4 -

A.   Approaches Used to Formulate
      Sustained-Release Oral Suspensions

The formulation of oral suspensions that exhibit
sustained-release activity presents many challenges
due to the substantial loss of the biologically active
ingredient to the surrounding suspending medium during
storage. Different approaches have been undertaken in
the past to overcome this problem (Chang, *Pharm.
Technol.*, 16(Mar):134 and 136 (1992)). The following
is a brief discussion of each of the different
strategies utilized:

1.   Sustained-Release Suspensions
      Of Poorly Water-Soluble
      Biologically Active Ingredients

Different microencapsulation techniques, such as
spray congealing, spray drying, solvent evaporation,
etc., can be used to prepare slow-release
microencapsulated particles for incorporation in a
suspension dosage form. The amount of biologically
active ingredient leaching out during the shelf-life
is minimized because of the low solubility of the
biologically active ingredient in the aqueous
suspending vehicle. However, there is always a
concern that the biologically active ingredient could
continue to leach out of the sustained release
coating, resulting in significant physical instability
which might be accompanied by chemical instability if
the biologically active ingredient is susceptible to
hydrolysis in the suspending medium. Moreover, this
technique can only be utilized for poorly
water-soluble biologically active ingredients.

The preparation of a slow-release, fine
monolithic matrix containing the biologically active
ingredient for incorporation into suspending vehicles
has been described (Robinson et al, *J. Am. Pharm.*

- 5 -

Assoc., Sci. Ed., 47:874-878 (1958); and Smith et al, *J. Pharm. Sci.,* 59:776-779 (1970)). Poorly water-soluble biologically active ingredients, such as sulfonamide and dextromethorphan, were dispersed in a molten wax, and the mixture was congealed by spraying under controlled conditions. Sulfamethylthiadiazole (Robinson et al, *supra*) mixed with hydrogenated caster oil heated to 140°C was spray congealed to yield powder with an average surface diameter of 34 μm. A second sustained release powder of sulfamethylthiadiazole was prepared by mixing it with glyceryl distearate melted at 80°C, followed by cooling and milling. A poorly water-soluble salt of dextromethorphan (Smith et al, *supra*) was crystallized from different solvent systems and was coated with a triglyceride fatty acid mixture. The coated crystals were dispersed in an aqueous suspension to yield a stable suspension having prolonged *in vitro* release.

　　　　　2.　　Saturated Drug Suspension as a
　　　　　　　　Suspending Medium

A method of preparing sustained-action liquid dosage forms for various compounds by microencapsulating the biologically active ingredient and subsequently suspending the microencapsulated form in a vehicle saturated with the biologically active ingredient has been described (Carrais, U.S. Patent 4,902,513 (1990)).

Saturation of the vehicle with the biologically active ingredient prevents undesirable leaching from sustained-release microcapsules during storage. The biologically active ingredient in the saturated solution provides the immediately available portion for absorption. The medication in the microencapsulated reservoir is designed to be released

- 6 -

at a relatively slow rate. However, for such a system, fluctuations in the storage temperature may result in appreciable nucleation, crystal growth, and alteration in dissolution profiles.

3. Non-aqueous Vehicles

The use of oleaginous vehicles, such as almond oil, sesame oil, sunflower oil, etc., for the preparation of oral liquid suspensions has been described (Mulligan, European Patent 295,941). The enhanced bioavailability, improved absorption characteristics, and reduced intersubject variability have been demonstrated for various biologically active ingredients including amoxicillin trihydrate, dextromethorphan, erythromycin ethyl succinate, guaifenesin, potassium chloride, prednisolone, and roxithromycin.

Thus, the biologically active ingredient loss into the suspending vehicle can be eliminated by minimizing the solubility of the biologically active ingredient in the suspending vehicle, or by choosing a vehicle which does not cause the biologically active ingredient to leach during storage. However, oily suspending vehicles or non-aqueous solvents could potentially act as plasticizers for the polymeric membrane coating responsible for sustaining or delaying the biologically active ingredient action, and thus could cause an unwanted change in its permeability characteristics.

4. Protective Coatings

Enteric coatings are usually intended to release the biologically active ingredient after some time delay, or after the tablet has passed through one part of the gastrointestinal (GI) tract into another.

- 7 -

Enteric protective coatings can be utilized to extend
the shelf-life when a product is stored in an aqueous
acidic medium (Ghebre-Sellasie, *supra*). However, upon
ingestion, the coatings are designed to break down,
and the drug is released from particles over a period
of time.

Controlled-release   liquid   suspensions   of
dual-coated dosage   forms   have   been   developed
(Benton et al, U.S. Patent 4,876,094). Biologically
active ingredient-loaded microparticles or matrix
beads with a particle size of less than 1400 μm were
coated with two layers prior to suspending them in a
sugar-based acidic vehicle.   The first coating
consisted of an ingestible hydrophobic fat having a
melting point of 101°F or lower. Low melting fats
were selected such that the materials would become
softened at body temperature, thus rendering the
coating permeable after ingestion.   Various fatty
materials and glycerides, such as cocoa butter and
partially hydrogenated vegetable oils and their blends
could be applied as the first coat. The second layer
consisted of zein or the enteric polymer cellulose
acetate phthalate.   The overcoat materials were
insoluble in the suspending medium, but became readily
permeable in the GI tract.   This dual coating
technique has been used successfully in the
formulation of a controlled-release suspension of
vitamin C, a highly water-soluble unstable compound,
as well as antihistamines and analgesics. However,
long-term studies on the stability of the suspensions
are not available.

- 8 -

5. Reconstitution

Ready-made suspensions might be associated with chemical instability of the biologically active ingredient or with some physical instability, such as cacking tendencies and dissolution profile changes. In such instances, a reconstitutible suspension can be always considered. This approach has been widely implemented in antibiotics intended for immediate release delivery of biologically active ingredients, but has never been used for sustained release delivery of biologically active ingredients. However, the increased cost and packaging problems of such units can be a limiting factor (Katare et al, *Indian J. Pharm. Sci.*, 50:19 (1988)).

6. Optimizing Vehicle Composition

The use of syrups of varying water concentration for liquid pharmaceuticals is widespread. Previous studies have shown that the solubility of a given compound in syrup may be significantly different from water (Shihab et al, *J. Pharm. Sci.*, 77:455-457 (1988); Valdez et al, *J. Pharm. Sci.*, 57:2093-2096 (1968); Paruta, *J. Pharm. Sci.*, 53:1252-1254 (1964); and Paruta et al, *J. Pharm. Sci.*, 55:1208-1211 (1966)). It has been found that increasing the concentration of sucrose, glucose, or sorbitol tends to decrease the solubility of sorbic acid in aqueous vehicles by decreasing the activity of water (Shihab et al, *supra*). Calculation of the free energy and enthalpy changes indicated that the dissolution process for sorbic acid became progressively unfavorable upon increasing the sugar concentration. The effect of polarity and dielectric constants of the dissolution media on the solvency characteristics of

- 9 -

syrup vehicles on some relatively nonpolar biologically active ingredients, such as quinine alkaloids, phenobarbital, PABA, and sulphanilamide was investigated (Paruta, *supra* (1964)). Solubility increased upon increasing the sugar concentration. This can be explained on the basis of decreasing polarity of the syrup vehicles upon increasing the sugar concentration. A syrup may be selected to exhibit lower biologically active ingredient solubility in the vehicle.

7. *In Situ* Gelling Mechanisms

Novel oral liquid theophylline formulations that were transformed from the liquid state to a matrix gel in the environment of the stomach and produced prolonged release of the biologically active ingredient have been developed (Zatz et al, U.S. Patent 4,717,713). The utilization of some macromolecular excipients is known to influence biologically active ingredient dissolution and biological availability. This may result from complexation with the biologically active ingredient, increasing bulk viscosity in the digestive tract or delaying the breakup of granules into smaller particles. Gelling agents used in the study included xanthan gum, sodium alginate, gelatin, carrageenan, methyl cellulose, and mixtures thereof, in amounts varying from approximately 0.3 to 5.0% by weight of the vehicle. Useful vehicles include aqueous, mixed and non-aqueous solutions or suspensions of the gelling agents. After gel formation, biologically active ingredient release from the preparation was controlled by diffusion of the biologically active ingredient through the gelatinous matrix.

- 10 -

Gas-producing salts, such as calcium carbonate and other carbonates could be incorporated in the formulation to produce a "floating" gelatinous matrix, which could potentially prolong the retention of the dosage form in the stomach.

8. Ion-Exchange Resins

Ion-exchangers are solid high-molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion-exchange is reversible and stoichiometric, with the displacement of one ionic species by another. Ion-exchange resin-biologically active ingredient complexes have been used to formulate sustained release products of acidic or basic biologically active ingredients (Keating, U.S. Patent 2,990,332; Raghunathan, U.S. Patent 4,221,778; Raghunathan et al, *J. Pharm. Sci.*, 70:379-384 (1981); and Amsel et al, *Pharm. Technol.*, 8(4):28-48 (1984)). The ion-exchange resin consists of two principal parts: a structural portion consisting of a polymer matrix, usually styrene cross-linked with divinyl benzene, and a functional portion which is the ion-active group to which the biologically active ingredient is bound. The functional group may be acidic (sulfonic or carboxylic) or basic (usually amine). When the polymer-biologically active ingredient complex is swallowed, the reverse reaction takes place, and the biologically active ingredient is liberated. The ion-exchange resins system, also known as Pennkinetic® system, was considered as a technical break-through that has made it to the market. However, this technique has its own limitations, such as the possibility of low biologically active

ingredient-loading capacity, and the applicability only to ionic biologically active ingredient species. Delsym® is a commercial example of a dextromethorphan Pennkinetic® suspension currently available in the market.

9.   Rapidly Disintegrating Tablets for the Formation of Instantaneous Immediate or Sustained Release Suspensions

Although oral formulations comprising particles of an biologically active ingredient suspended in a viscous aqueous vehicle have been previously described, these compositions are formulated as ready-to-use suspensions from the outset and are handled, transported and stored as such. Formulations have been patented (Benzon, U.S. Patent 5,147,655; Ventouras, European Patent 0-273-055; and Ventouras et al, U.S. Patent 4,886,669) in which the product is stored in a ready-to-use dry form, and converted to a suspension by adding an aqueous carrier or pre-mixed gel. This presents the important advantage of increased storage stability over a premanufactured suspension, and permits a wider range of active substances to be incorporated. Moreover, it provides improved packaging, handling and transportation properties due to the fact that the ready-to-use suspension is prepared *in situ* by the end user. Furthermore, it is easy to measure out the exact dosages of the biologically active ingredient because the particles comprising the biologically active ingredient are present as dry powders, tablets or capsules in a unit dosage form. Such formulations make it possible to administer large individual dosages of a biologically active ingredient in that

- 12 -

they do not impose size limitations, as do
conventional tablets or capsules.

A description of the composition and manufacture
of powders for suspension is found in Benzon, *supra*.
This patent primarily deals with powders and presents
only one example of a tabletted product involving
coated potassium chloride crystals which deform
plastically to produce strong tablets. Moreover, most
of the examples given in this patent involve the
admixture of the biologically active ingredient-loaded
particles with a premixed viscous gel medium. The use
of powders either in bulk or as premeasured doses are
much less convenient than tablets or capsules.

A water-dispersible tablet containing
biologically active ingredient-loaded microparticles,
a disintegrant, and a swellable material capable of
generating a high viscosity when coming in contact
with water was described previously (Ventouras, *supra*;
and Ventouras et al, *supra*). On contact with water,
the tablet disintegrates "rapidly" to surpass the
opposite swelling effect caused by the viscosity
enhancer. After the tablet has disintegrated in
water, the viscosity enhancer swells, resulting in a
homogenous suspension consisting of biologically
active ingredient-loaded beads. The disintegration
time of the tablets produced by these patents was
between one and two minutes, which can result in
viscosity build-up within the tablet matrix before
disintegration, whereby incomplete dispersion occurs.
These patents used dry granules of MCC and lactose
prepared by slugging as the filler binder. Dry
granulation of MCC tends to decrease its
compactibility. Moreover, the presence of lactose, a
water-soluble excipient, prolongs the disintegration

- 13 -

time. These patents did not claim sustained release as a possible application but, rather, used coated micropellets of methylxanthines.

In order to formulate a self-disintegrating tablet to be dispersed extemporaneously in an aqueous carrier to deliver sustained-release biologically active ingredient-loaded pellets, it is essential that such tablets exhibit the following properties:

    (1) Possess a quickly hydrating swellable material incorporated in aggregates, such as granules or spheres, that allow the tablet to disintegrate first followed by viscosity build-up; and

    (2) Possess a filler system to be mixed with the sustained-release biologically active ingredient-loaded pellets and the viscosity enhancer needed to form a tablet. This filler should have minimal segregation propensity (similar size, density, and shape), and should cushion the sustained-release biologically active ingredient-loaded pellets to prevent dose dumping.

B. Formulation of Suspensions

General considerations to be addressed during the development of conventional biologically active ingredient suspensions also apply to the development of sustained-release suspensions (Bodemeier et al, *Multiparticular Oral Delivery Drug* (Ghebre-Sellassie) Mercel Dekker, New York, NY, pages 143-157 (1994)). These considerations include the selection of proper suspending vehicles, suspending agents, surfactants, flavoring agents, preservatives, and other ingredients

- 14 -

to formulate a stable, elegant, and pharmaceutically acceptable dosage form.

The principle or theory of suspensions has been described extensively in numerous articles and reviews (Kennon et al, *The Theory of Practice of Industrial Pharmacy*, (Lachman et al, Eds.), Lea & Febiger, Philadelphia, PA, pages 162-183 (1976); Falkiewics, *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman et al, Eds.), Mercel Dekker, New York, NY, Volume 1, pages 13-48 (1988); Nash, *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman et al, Eds.), Mercel Dekker, New York, NY, Volume 1, pages 151-198 (1988); and Offner III et al, *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman et al, Eds.), Mercel Dekker, New York, NY, Volume 2, pages 231-264 and 317-334 (1989)). Important characteristics for sustained-release suspensions containing biologically active ingredient-loaded spheres or microparticles are listed below:

    (1) Excipient selection: A typical suspension contains a wetting agent, suspending agent, flocculating agent or protective colloid, sweetener, preservative, buffer system, flavoring agent and coloring agent.

    (2) Reduced sedimentation rate: Modification of the particle size and/or the viscosity of the liquid medium have been the most popular approaches employed to improve suspension stability. The particle size of the spheres or microparticles can be controlled by using a

smaller-size extrusion screen for pellets produced by extrusion-spheronization, or by varying the agitation rate with microparticles formed by emulsification processes (e.g., solvent evaporation, melt dispersion, and interfacial polymerization methods), or by the atomization conditions with microparticles formed by spray drying or spray congealing. With respect to the dispersion medium, an inverse relationship exists between the rate of particle settling and the viscosity of the external medium.

C. Gelling Agents

Gelling agents are usually substances which form colloidal dispersions in an aqueous environment, the colloidal particles forming a three-dimensional network or grid-like structure throughout the liquid phase. The viscous gel medium may be one which becomes less viscous or dissolves in response to pH changes or enzymes degradation, such that diffusion through the gel does not influence the release of active substance from the particles.

Examples of useful gelling or swelling agents are hydrophilic polymers, such as pectin agar, carrageenan, acacia gum, guar gum, xanthan gum, alginic acid and acrylic acid polymers, such as carbomers.

- 16 -

1.   <u>Carbomers</u>

Carbomer resins (B.F. Goodrich literature, Cleveland, OH) are crosslinked acrylic acid polymers. The molecular structure of carbomer resins in the partially and fully solvated states are depicted in Figures 1A and 1B, respectively. A high percentage of carboxylic acid groups allow the resins to be water-swellable. In the presolvated dry state, a molecule of carbomer is tightly coiled. When dispersed in water, carbomer begins to hydrate and uncoil, resulting in partial build-up of viscosity. The molecule must completely uncoil to achieve the highest and most consistent viscosity. This is accomplished by neutralizing the polymer with a base. Neutralization with a water-soluble base ionizes the resin, generating negative charges along the polymer backbone. Repulsion of these negative charges causes expansion of the molecule, thereby causing the molecule to rapidly thicken. Overneutralization by strong bases can collapse the resin structure, resulting in a permanent loss of viscosity. The dissociated individual resins vary by molecular weight, degree of crosslinking and molecular architecture. These differences are responsible for the specific rheological characteristics and thickening efficiency of each carbomer resin.

Carbomers 934P (60 ppm benzene), 971P and 974P are the pharmaceutical grades used in oral, topical and novel biologically active ingredient delivery applications. They are unneutralized molecules which require the addition of a base to achieve maximum viscosity. Two neutralized versions of carbomers have been recently introduced into the market. EX161 and EX214 are salts of the 934P and 974P grades which do not require the addition of a base.

- 17 -

        In solid dose formulation, carbomer has been used
as dry tablet binder (Vila-Jato et al, *Int. J. Pharm.*,
30:229-236 (1986)), and as controlled release agent
via a hydrophilic matrix mechanism. Several papers
dealing with these products have been published
demonstrating their utility in achieving sustained
release with diverse active principles
(Vila-Jato et al, *supra*; Choulis et al, *J. Pharm.*
Sci., 64(6):1033-1035 (1975); Choulis et al,
Pharmazie, 31(Jul):466-470 (1976); Salib et al, *Pharm.*
Ind., 45(9):902-906 (1983); Agabeyoglu, *Drug. Dev.*
Ind. Pharm., 12(4):569-576 (1986); Graf et al, *Pharm.*
Ind., 48(6):661-665 (1986); Malley et al, *Drug Dev.*
Ind. Pharm., 13(1):67-79 (1987); Bulut-Öner et al,
Farmaco, 44:739-742 (1989); Capan et al, *Pharm. Ind.*,
51:443-448 (1989); Baun et al, *Pharm. Acta Helv.*,
46:94-113 (1971); Çiftçi et al, *Pharm. Res.*,
7(4):359-363 (1990); Pérez-Marcos et al, *Int. J.*
Pharm., 67:113-121 (1991); and Durrani et al, *Drug*
Dev. Ind. Pharm., 20(15):2439-2447 (1994)). These
papers deal exclusively with the 934 type of resin.
Some research papers have focused on the possibilities
that are offered by controlling the release of
hydrosoluble substances when used in conjunction with
hydroxypropyl cellulose (Satoh et al, *Chem. Pharm.*
Bull., 37(6):1642-1644 (1989)). Their practical value
is evident from various patents (Decrosta et al, U.S.
Patent 4,666,705; Ueda et al, Japanese
Patent 6,277,335; and Hirofumi et al, Japanese
Patent 63,101,332). Moreover, carbomer has been used
in the preparation of microcapsules intended for
sustained release delivery of biologically active

ingredients (Salib et al, *supra*; and El-Egakey et al, *Drug Dev. Ind. Pharm.*, 9(5):895-908 (1983)).

In liquid oral dose formulations and topical applications, carbomer has been utilized for its rheological modification properties to thicken a wide range of aqueous and alcoholic solutions, to suspend insoluble ingredients and to stabilize emulsions (Plazier-Vercammen et al, *Pharmazie*, 46:646-650 (1991); Banga et al, *Drug Dev. Ind. Pharm.*, 15(5):691-704 (1989); El-Assasy et al, *Drug Dev. Ind. Pharm.*, 11(1):65-81 (1985); Soci et al, *J. Pharm. Sci.*, 69(4):403-406 (1980); Ruiz et al, *Farmaco*, 49(Feb):147-152 (1994); Touitou et al, *J. Pharm. Sci.*, 81(Feb):131-134 (1992); Chawdry et al, *Indian Drugs*, 31(Jan):36-40 (1994); Demou et al, *Pharm. Acta. Helv.*, 68(May):215-219 (1994); Banga et al, *Pharm. Res.*, 10(May):697-702 (1993); Taylor, *Cosmet-Toiletries*, 93(Apr):71-73 (1978); Mercado et al, *Drug Dev. Ind. Pharm.*, 19(8):887-902 (1993); González et al, *Int. J. Pharm.*, 104:107-113 (1994); Amin et al, *Drug Dev. Ind. Pharm.*, 20(7):1309-1316 (1994); Dal-Zotto et al, *Farmaco*, 46(Dec):1459-1474 (1991); Baichwal et al, *Indian J. Pharm. Sci.*, 51(5):178-181 (1989); and Morimoto et al, *Drug Dev. Ind. Pharm.*, 13(7):1293-1305 (1987)). In novel biologically active ingredient delivery systems, carbomer has been used successfully in bioadhesives intended for the buccal, nasal, vaginal and rectal cavities (Harris et al, *J. Controlled Release*, 12(Mar):45-53 (1990); Anlar et al, *Pharm. Res.*, 11(Feb):231-236 (1994); Vidgren et al, *Drug Dev. Ind. Pharm.*, 18(5):581-597 (1992); Smart, *Drug Dev. Ind. Pharm.*, 18(2):223-232 (1992); Chu et al, *Pharm. Res.*, 8(Nov):1408-1412

- 19 -

(1991);   Nagai et al,   *Pharm.   Int.*,   6(Aug):196-200
(1985); and Morimoto et al, *J. Pharm. Pharmacol.*,
37(Feb):134-136 (1985)).   Carbomers are compatible
with most of the ingredients used in personal care and
pharmaceutical formulations.   Soluble salts, such as
sodium chloride, decrease the efficiency of carbomer
resin mucilage.   All monovalent cations affect
carbomer resins similarly.   Divalent and trivalent
cations cause a more drastic loss in the ability of
carbomers to build-up viscosity (Charman et al, *Drug
Dev. Ind. Pharm.*, 17(2):271-280 (1991)).

Carbomer resins not only thicken solutions, but
also provide a wide range of flow properties.   Like
numerous polysaccharide thickeners, such as modified
cellulosics and natural gums, carbomer resins are
shear   thinning   (the   viscosity   decreases   with
increasing shear rate).   However, unlike most linear
polysaccharides,   carbomer   resins   display   plastic
rheological profiles.   Carbomer solutions will not
flow until a minimum force, called the yield value is
reached.   Carbomer resins provide excellent stability
to oil-in-water (o/w) emulsions and suspensions. When
used   in   conjunction   with   appropriate   emulsifying
agents and coemulsifiers, carbomer resins provide long
term stability at ambient and elevated temperatures,
as well as under freeze-thaw conditions.   The yield
value created by carbomer resins prevents "creaming"
or separation of o/w emulsions by suspending and
separating the oil droplets.   It also allows particles
to be permanently suspended throughout the medium,
creating stable non-settling products, even when used
at very low concentrations.

One of the major difficulties encountered with
carbomer, as well as with other hygroscopic powders,

is its poor dispersibility. These dry powder resins
are highly hygroscopic and hydrate rapidly when added
to water or polar solvents. Thus, carbomer resins
will clump or incompletely hydrate when haphazardly
introduced to polar media. The surfaces of these wet
agglomerates quickly solvate and form a layer which
prevent rapid wetting of the dry interior. This,
together with the fluffy nature of carbomer, results
in dispersion defects, such as grainy texture, reduced
viscosity   or   the   presence   of   partially   wet
agglomerates. Therefore, to avoid lengthy mixing
times and to prepare high quality, reproducible
carbomer resin dispersions, either proper dispersion
techniques should be utilized or carbomer should be
formulated in a readily dispersible less fluffy form,
such as granules or spheres, or powder-layered on the
surface of carrier seeds.

D.   Powder-layering

Powder-layering can be traced to the 1956 patent
by Blythe (U.S. Patent 2,738,303). This process
involved layering a drug powder onto nonpareils using
syrup as the adhesive solution. There have been
40 years of research and development experience in the
powder-layering technology, and a wide variety of
products have been successfully developed and
introduced into the market.

The term "layering" (Parikh, "Layering in Rotary
Fluid Bed: A Unique Process for the Production of
Spherical Pellets for Controlled Release", Presented
in Interphex-USA (May 18, 1991)) involves the
deposition of successive layers of a compound from
solution/suspension or dry powder on core particles,
which may be crystals or granules of the same material
or an inert starter core, such as nonpareil seeds. In

solution/suspension systems, the biologically active
ingredient particles are dissolved or suspended in the
binder solution.   As the liquid evaporates, the
dissolved substances crystallize out.   On further
evaporation, these crystals, or the particles that are
initially suspended in the binder solution, are drawn
toward each other and towards the starter core by
capillary forces. The limitations of this process are
that there is a limit to the amount of the
biologically active ingredient which can be mixed with
the binder solution, a problem with the removal of
large quantities of liquid from the layered beads, and
the possibility of recrystallization from the solution
while drying.

     In powder-layering, the biologically active
ingredient does not come in contact with the binder
solution until it is sprayed onto the inert seed
material, as the binder and biologically active
ingredient are sprayed from different ports. As the
amount of binder solution needed is much less when
compared to other layering techniques, drying will be
very fast and the total process is much faster than
the other processes.

     The Aeromatic® rotoprocessor (see Figure 2) is
the latest development used in the powder-layering
process.   It is a modified fluid bed equipped with a
spheronizer-like wheel.   It utilizes frictional,
centrifugal and gravitational forces, which are all
induced by the rotary disc. The fluidized air affords
efficient evaporating capacity.   It consists of an
inner and outer process chamber, called forming and
drying zones, respectively, separated by a straight
wall. The lower part of the forming zone is a rotary
disc similar to the one in the spheronizer with a cone
in the middle. The surface of the disc can be either

- 22 -

smooth or textured. Beneath the rotary disc there is
flushing air whose function is to prevent the product
from depositing between the disc and the wall, and
from penetrating the lower part. The straight wall
can be pneumatically lifted allowing the product to
pass into the outer drying zone. The drying zone is
annular, and has a stationary perforated bottom
through which preheated air flows upwards, drying the
product as it is transferred from the forming zone to
the drying zone by the centrifugal forces created by
the rotary disc.

E.   Extrusion-Spheronization

Extrusion and spheronization, as a process for
the manufacture of multi-particulates, has gained
increased usage during the past decade because of the
increased popularity of multi-particulate controlled
release oral dosage forms (Nesbitt, *Drug Dev. Ind.
Pharm.*, 20(20):3207-3236 (1994)). Although proposed
originally as a novel process, the mechanical
mechanisms that produce a spherical multi-particulate
using the extrusion-spheronization process are similar
to those once used by the traditional pill making
process (Rowe, *Pharm. Int.*, 6:119-123 (1985)).

Spheronization was invented in 1964 by Nakahara
(U.S. Patent 3,277,520). The process was not widely
known until two review articles were published in 1970
by the Eli Lilly organization (Conine et al, *Drug
Cosmet. Ind.*, pages 38-41 (April, 1970); and Reynolds,
Manuf. Che. Aerosol News, 41:40-43 (1970)). Equipment
design change has been minimal since the original
patents. The spheronizer consists basically of a
grooved horizontal plate rotating at high speed within
a stationary vertical cylinder fitted with a door to

allow release of the pellets.   Although extrusion is usually regarded as a continuous process, spheronization equipment design limits the extrusion-spheronization process to a batch process or a multiple batch process.

5

There are five unit operations involved in the extrusion-spheronization process.   These are: blending, granulation, extrusion, spheronization and drying. The moistened pre-compacted mass is extruded into strands, which are then rounded into pellets in a spheronizing machine, dried and subjected to further processing. The moisture content and composition of the mixture must be carefully selected in order that the desired plastic deformability (extrudability) is obtained. The particle size distribution of the pellets obtained is primarily determined by the extrudate density and water content (Dietrich, *Manuf. Chem.*, 60:29-33 (1989)).

10

15

Early workers in the extrusion-spheronization field always included MCC in their example formulas for use with this technique (Conine et al, *supra*; and Reynolds, *supra*).   Miyake et al (*Yakazaigaku*, 33:161-166 (1973)) reported in 1973 that MCC exhibited the elasticity required for extrusion-spheronization, whereas corn starch and lactose could not be extruded and spheronized when mixed with various quantities of water. Additional work done by Harrison and coworkers (Harrison et al, *J. Pharm. Pharmacol.*, 37:686-691 (1985)) demonstrated that MCC has the ability to take up water into its intraparticulate voidage and become readily deformable.   It was also shown that this excipient is insensitive to moisture concentration changes when compared to water-soluble crystalline material, such as lactose.

20

25

30

- 24 -

1. **Effect of the Amount and Composition of Granulation Liquid on the Characteristics of Spheres Produced by Extrusion-Spheronization**

The amount and type of granulating fluid used to prepare extrudable masses has a major influence on the different properties of the spheres produced. Beart et al (*Int. J. Pharm.*, 95:135-141 (1993)) found that the amount of granulating fluid used had an influence on biologically active ingredient release from the pellets. A slower release was observed with increasing amounts of granulation fluid. These differences in release profiles were correlated with differences in hardness, density and structure of the pellets. Otsuka et al (*Drug. Dev. Ind. Pharm.*, 20(19):2977-2992 (1994)) attributed the change of the mechanical strength of the spherical granules produced using different quantities of water to difference in the internal porosity of the fluid-bed dried granules. Friability decreased with increasing the amount of granulating water added. On the other hand, the hardness of the tablets prepared from such granules seem to be inversely related to the strength of the intact granules. Thus, tablets prepared from harder granules showed a capping tendency.

The effect of changing the granulating liquid composition on the mechanical properties of granules was studied by Millili et al (*Drug Dev. Ind. Pharm.*, 16(8):1411-1426 (1990)). It was found that a difference in the release rate exists for pellets prepared with MCC and theophylline and granulated with different proportions of ethanol/water, but where the same amount of granulating fluid was used. Pellets prepared with higher percentage of water showed slower

- 25 -

release, lower porosity, greater hardness and less
compactibility.

The amount of granulating liquid is usually
affected by the composition of the formulation. More
granulating liquid is required as the level of MCC is
increased (Elber et al, *Drug Dev. Ind. Pharm.*,
18(5):501-517 (1992)). Pinto et al (*Int. J. Pharm.*,
83:187-196 (1992)) studied the effect of different
formulation and processing variables on the shape and
size distribution of the spheroids, the drug release
profile and the force required for steady-state
extrusion, and found that the most important factor
was the water content, in particular the water content
at the die wall during extrusion. Factors which may
be expected to decreased the water availability at the
die wall (i.e., decreased water and decrease MCC
content) were found to have a detrimental effect on
the product in terms of size and size distribution.
Formulations with higher water content were found to
have the most significant variation in size, i.e., as
the water content increases, the median sphere size
and size distribution increase. Thus, changing the
moisture content of the wet granulated mass prior to
extrusion-spheronization (Hasznos et al, *Drug Dev.
Ind. Pharm.*, 18(4):409-437 (1992)) has a major impact
on the size and size distribution, as well as on other
physico-mechanical and release properties of the
spheres. Therefore, choosing the optimum granulating
fluid level is of great importance to the production
of spheres by extrusion-spheronization.

- 26 -

2.   Characterization of the Optimal
     Liquid Level Suitable for
     Extrusion-Spheronization

Wet powder masses intended for extrusion and
spheronization must have specific rheological
requirements which are largely affected by the type
and amount of both of the solid ingredients, as well
as the granulating fluid.

Optimum conditions for the
extrusion-spheronization process can be determined by
measuring the plasticity of the biologically active
ingredient-excipient mixture as a function of the
amount of granulation liquid added.   A technique
developed by Alleva et al (*Drug Dev. Ind. Pharm.*,
<u>12(4)</u>:471-478 (1986)), directed towards the
characterization of the granulation step prior to
extrusion, was based on the principle of measuring the
force granulation exerts on a load cell when the
wetted material is stressed.   This technique was
utilized by Elber et al, *supra*, to study the
extrudability of MCC containing sodium carboxymethyl
cellulose as a binder (Avicel® RC 581).

Most commercial extruders do not allow for
rheological measurements.   The ram extruder provides
a suitable alternative and lends itself to application
of theory derived from capillary rheometry.
Harrison et al (*J. Pharm. Pharmacol.*, <u>37</u>:686-691
(1985)) used that system to characterize the
rheological behavior of wet powder mixtures used in
the extrusion-spheronization process.
Force/displacement (flow rate/shear stress) curves
were obtained for materials forced through dies in
order to determine the quantity of water needed to
form an extrudable mixture.   It was found that the
force/displacement curves exhibit three stages,

- 27 -

namely: compression, steady-state flow and forced
flow. The steady-state stage provided the highest
quality extrudate. The usefulness of this technique
for evaluating the suitability of preparations for
5   processing has been established by many workers
(Fielden et al, *J. Pharm. Pharmacol.*, 41:217-221
(1989); Fielden et al, *Int. J. Pharm.*, 81:205-224
(1992); and Bains et al, *Int. J. Pharm.*, 69:223-237
(1991)).

10   Shah et al (*Pharm. Research*, 11(3):355-360
(1994)) proposed an objective measure of extrudability
of materials by monitoring the extrusion screen
pressure and temperature induced by the stress used to
force the wet mass through the small orifice, and
15   frictional heat build up, respectively.

If a more critical evaluation of the product is
required, it is necessary to consider size and range
of sizes produced by the process. A preparation that
is too dry is difficult to extrude and results in
20   anisomeric particles, whereas that which is too wet
results in gross agglomeration on the spheronizer
plate, leading to grossly enlarged agglomerates. At
an optimum water level, nearly spherical particles are
usually obtained. Thus, image analysis of the freshly
25   produced pellets can be used to determine the optimum
water level (Kleinebudde, *Int. J. Pharm.*, 96:119-128
(1993); Kleinebudde, *Int. J. Pharm.*, 109:209-219
(1994a); and Kleinebudde, *Int. J. Pharm.*, 109:221-227
(1994b)).

- 28 -

F. Effect of Drying Conditions on on Physico-Mechanical Properties of Spheres

There is a remarkable difference in the physico-mechanical properties of pellets as a result of the drying technique. Kleinebudde (1994a), *supra*, compared freeze-drying, fluid-bed drying and oven drying. It was found that only a minor shrinking tendency can be seen during freeze-drying. Removing the water leaves a skeleton of solid materials with resultant freeze-dried pellets having similar size to the wet pellets, as well as high porosities. Evaporation of water in an oven or in a fluid bed is accompanied by a shrinking process. The resultant pellets are smaller than the wet ones, and are more dense.

Betaille et al (*Drug Dev. Ind. Pharm.*, 19(6):653-671 (1993)) compared two drying processes namely: oven and microwave drying. Microwave drying led to higher porosities compared to oven drying. Oven drying is considered to be a slow and less traumatic process, while microwave drying will lead to a quicker loss of water. During the microwave drying, shrinking of the matrix may be incomplete due to the rapidity of the process.

Dyer et al (*Drug Dev. Ind. Pharm.*, 20(20):3045-3068 (1994)) compared tray-drying and fluidized bed-drying of pellets containing MCC and lactose produced by extrusion-spheronization. The differentiating factor between the two processes is the rate of water removal from the spheres. The pellets dried by the fluidized-bed technique achieve the desired moisture content much more quickly due to the rapid evaporation of water, as a result of the turbulent motion of the air and the fluidized

- 29 -

particles.   In tray-drying, the water removal from
dried material is slow due to the static nature of the
technique. The free movement of individual fluidized
particles lead to rapid migration of solute particles
(lactose dissolved in the granulating water) within
the spheres; those tray-dried entities are more likely
to exhibit solute migration during the lengthy drying
process.   Thus, it was concluded that the drying
method employed has a significant effect on the
mechanical strength of the product prepared by
extrusion-spheronization.   The solubility of the
excipients from which the pellets are composed affects
the degree of solute migration occurring during
drying.   For beads containing water, and soluble
materials such as lactose, it is not unreasonable to
anticipate the presence of solute molecules of this
component which have dissolved in the aqueous
granulating fluid during the wet massing stage. Water
removal from those beads during drying following
spheronization would thus, lead to the formation of
solid bridges within the spheres by fusion at the
points of contact of the primary powder particles.
This will result in a greater degree of bonding and
hence, the formation of beads of greater strength than
if the amount of lactose was replaced by a
biologically active ingredient with poor water
solubility, such as ibuprofen (Aulton et al, *Drug Dev.
Ind. Pharm.*, 20(20):3069-3104 (1994)).

1.   Freeze-Drying
Freeze-drying or lyophilization (FTS Systems,
Inc., Instruction Manual, Stone Ridge, NY, pages 1-20
(1991)), is in simple terms a dehydration technique.
The aspect of the freeze-drying process that makes it

- 30 -

different is that dehydration takes place while the product is in a frozen state and under vacuum. There are four basic steps in freeze-drying: Pretreatment (usually confined to biologicals), freezing, primary drying, and secondary drying, all of which are important to the success of the freeze-drying run.

In order to freeze a product properly, thermal analysis of the product must be conducted. Water has a freezing point of 0°C. Almost any product that has a constituent other than water will experience a heat of fusion/crystallization not only around 0°C, but also at a reduced temperature. In the sphere matrix there is essentially "unbound or free" solvent. This is the solvent that is not closely associated with the product itself. The solvent that is more closely associated with the product will freeze at some reduced temperature. The reduction in freezing point of the solvent may be due to weak solvent/solute bond formation. Thus, in order to freeze-dry a product, in the perfect sense of the word, the product temperature must be maintained below its lowest freezing point during all of the primary drying step.

The rate of freezing plays an important role in determining the crystalline size, among other things. Since the solvent crystal will eventually be subliming out of the product, a larger crystalline structure will produce a more porous, and consequently more quickly dried, product.

The driving force of sublimation during the primary drying is the pressure differential between the product and the condenser of the freeze-drier created by a temperature differential. A law of nature is that as the temperature of water is decreased, the pressure over that water also decreases. A specific temperature of water is always

- 31 -

associated with a specific pressure. Thus, in order for a freeze-dryer to be effective, the temperature of the condenser must be lower than the temperature of the product. This temperature differential creates a pressure differential and the net migration of water vapor is towards the condenser, resulting in an increase in the condenser temperature. Therefore, primary drying is often a delicate balance between the energy input to the product and the pressure differential created between the product and the condenser due to the temperature differential.

When the product reaches a temperature above 0°C, secondary drying has begun. During secondary drying, the vacuum pump of the freeze-dryer creates the low pressure condition necessary for the removal of solvents. The solvent being removed in this phase is referred to as "bound" solvent. The amount of residual water in the product is dependent on the length of time the product remains in secondary drying.

G.   Coating Formulations for Modified
      Release Multi-particulates

Aqueous solutions of water-soluble polymers (methyl cellulose and hydroxypropyl methylcellulose) are suitable only for isolating layers or fast-disintegrating coatings, with limited use in controlled-release multi-particulate systems. Water-based systems have been developed for pharmaceutical dosage forms instead of organic-based polymeric solutions because of their environmental and economic advantages. Because water has a high heat of vaporization, aqueous systems that might require lengthy processing times seemed initially to have a serious economic disadvantages despite their

- 32 -

environmental advantages. However, in addition to the progress of fluidized bed technology, which reduced the lengthy processing times of aqueous based systems, the aqueous polymeric latexes and pseudolatexes that have been developed since the 1970's have overcome the disadvantages by their low-viscosities and high polymeric contents.

As with any film coating, the polymer has a key role in the properties and characteristics of a film intended to convey a modified release aspect on a multi-particulate system (Hogan, "Coating Formulations for Modified Release Multiparticulates", Fourth Symposium of the Pharmaceutical Compaction Research Laboratory and Information Center, Piscaraway, NJ (March 14, 1994)). Plasticizers are added to provide a desired modification in the mechanical properties of the polymer film.

1.   Controlled Release Polymers

a.   Ethylcellulose

Ethylcellulose is used extensively in modified release coatings from organic solvent based system alone or in combination with other cellulosic polymers, notably hydroxypropyl methylcellulose.

In many ways, ethylcellulose is an ideal polymer for modified release coatings. It is odorless, tasteless and exhibits a high degree of stability, not only under physiological conditions, but also under normal storage conditions being stable to light and heat. Commercially, ethylcellulose is available in a wide range of viscosity and substitution types, giving a good range of possibilities to be employed. It also possesses good solubility in common solvents used for film coating, but this feature is nowadays of lesser

- 33 -

importance with the advent of water dispersible
pseudolatex presentations of ethylcellulose which have
been especially designed for modified release
coatings. The polymer is not usually used on its own,
but normally in combination with secondary polymers,
such as hydroxypropylmethyl cellulose or polyethylene
glycols, which convey a more hydrophilic nature to the
film by altering its structure by virtue of pores and
channels through which biologically active ingredient
solution can more easily diffuse. The films formed
from ethylcellulose in organic solvents are very
effective in controlling the biologically active
ingredient release, and are still widely used in many
commercial products.

        b.   Methacrylate Ester Copolymers
        Structurally methacrylate ester copolymers bear
a resemblance to the methacrylic acid polymers, but
are totally esterified with no free carboxylic acid
groups (Manufacture's Literature, Rohm Tech Inc.,
Malden, MA). Thus, these materials are neutral in
character, and are insoluble over the entire pH range.
However, they do possess the ability to swell and
become permeable to water and dissolved substances.
Thus, they find application in the coating of modified
release dosage forms. Eudragit® RL is a
poly(ethylacrylate, methylmethacrylate,
triethylammonioethyl-methacrylate chloride) 1:2:0.2,
and has slight sustained release activity.
Eudragit® RS is a poly(ethylacrylate,
methylmethacrylate, triethylammonioethyl-methacrylate
chloride) 1:2:0.1, and has more sustained release
activity. The two polymers Eudragit® RL and RS can be
mixed and blended to achieve a desired release
profile. The addition of hydrophilic materials, such

- 34 -

as the soluble cellulose ethers, polyethylene glycols etc., will also enable modifications to be achieved with the final formulation. The polymer Eudragit® RL is strongly permeable, and thus only slightly retardant. For aqueous spraying, a pseudolatex form of the RL and RS polymers is available.

c.   True Latexes

True latexes are very fine liquid dispersions of polymer in an aqueous phase produced by emulsion polymerization. The process starts with a monomer which, after purification, is emulsified as the internal phase with a suitable surfactant. Polymerization is activated by the addition of an initiator. Using this process Eudragit® L30D (poly(ethylmethacrylate methacrylic acid) 1:1, 30% aqueous dispersion) and NE30D (poly(ethylacrylate, methylmethacrylate) 2:1, 30% aqueous dispersion) are produced. Eudragit® L30D and NE30D are commonly used in combination for enteric coating.

d.   Pseudolatexes

Commercially there are three main products which fall into the category of pseudolatexes, two of which utilize ethylcellulose as the polymer, while the third utilizes polymethacrylate copolymers. Characteristically, pseudolatexes are manufactured starting with the polymer itself and not the monomer. By a physical process, the polymer particle size is reduced, thereby producing a dispersion in water, the characteristics of which need not differ significantly from a true latex, including particle size considerations. The pseudolatex is also free of monomer residue and traces of initiator.

- 35 -

The earliest of the two ethylcellulose products (Aquacoat®), is manufactured by dissolving ethylcellulose in an organic solvent and emulsifying the solution in an aqueous continuous phase. The organic solvent is eventually removed by vacuum distillation, leaving a fine dispersion of polymer particles in water. Aquacoat® is composed of 30% (w/w) solids content of which 87% is ethylcellulose, 9.0% cetyl alcohol and 4.0% sodium lauryl sulfate. The cetyl alcohol and sodium lauryl sulfate act as a stabilizer and surfactant, respectively, and are added during later stages of production (Manufacture's Literature, FMC Corp., Malden, MA).

The newer of the ethylcellulose products is Surelease®, which is manufactured by a process based on phase inversion technology. The ethylcellulose is heated in the presence of dibutyl sebacate and oleic acid, and this mixture is introduced into a quantity of ammoniated water. The resulting phase inversion produces a fine dispersion of ethylcellulose particles in an aqueous continuous phase. The dibutyl sebacate is to be found in the ethylcellulose fraction, whilst the oleic acid and the ammonia together effectively stabilize the dispersed phase in water. Surelease®, unlike Aquacoat®, does not require the further addition of plasticizer. Surelease® also contains a quantity of fumed silica which acts as an antitack agent during the coating process. Its total nominal solid content is 25% (w/w) (Manufacture's Literature, Colorcon, West Point, PA).

Polymethacrylate copolymers, such as Eudragit® RL30D and RS30D, are composed of a 30% aqueous dispersion of polymethacrylate. These polymers are freely miscible in each other, and can be mixed and

- 36 -

blended to achieve a desired release profile
(Manufactures' Literature, Rohm Tech Inc., *supra*).

e.   Plasticizers

Plasticizers are relatively low molecular weight
materials which have the capacity to alter the
physical properties of a polymer so as to render the
polymer more useful in performing its function as a
film coating material. Plasticizers make the film
softer and more pliable. The mechanism of action of
plasticizers is that the plasticizer molecules
interpose themselves between the individual polymer
strands, thus breaking down, to a large extent, the
polymer-polymer interactions. This action is
facilitated as the polymer-plasticizer interaction is
considered to be stronger than the polymer-polymer
interaction.

One fundamental property of a polymer is the
glass transition temperature (Tg). This is the
temperature at which a polymer changes from a hard
glassy material to a softer rubbery material. The
action of the plasticizer is to lower the glass
transition temperature.

The commonly used plasticizers can be categorized
into three groups; the polyols (glycerol, propylene
glycol and polyethylene glycol), organic esters
(phthalate esters, dibutyl sebacate, citrate ester and
triacetin) and oils/glycerides (caster oil, acetylated
monoglycerides and fractionated coconut oil).

2.   Assessment of the Mechanical
Properties of Polymeric Films
Used to Coat Multi-particulates

The assessment of the mechanical properties of
the polymer films used for coating of

- 37 -

multi-particulate spheres provides information which
will help to understand the ability of these films to
contribute to the deformation resistance of the
millispheres, and thus their ability to withstand the
stresses associated with their compaction into a
tablet matrix. Among the different approaches utilized
to assess the mechanical properties of the polymeric
films are indentation testing, and the percentage of
elongation of the free film before breakage.

Indentation testing provides a valuable means of
assessing the mechanical properties of the polymer and
the effect of the presence of other excipients within
the film.   This is fundamental to the further
understanding of the manner in which polymer films
will perform during tablet compression.   Among the
parameters which are particularly useful in this
respect is the elastic modulus of the polymeric film.
Those materials exhibiting a relatively low elastic
modulus will therefore, undergo a relatively high
instantaneous elastic strain at low loads during and
following compression.   This will confer a high
resilience to the millisphere, and reduce its
brittleness. Increasing the plasticizer content in a
given polymeric film formulation will increase the
permanent   non-recoverable   plastic   deformation
associated with the applied stress.   Moreover, in
addition to the polymer and plasticizer, the presence
of other excipients within a polymer film (e.g.,
opacifiers, and pigments) may also exert a
considerable influence on the mechanical properties of
a given polymer film formulation.

Aulton et al, *supra*, studied the effect of
plasticizers on the mechanical properties of
polymethacrylate films, and found that increasing the
plasticizer level would decrease the elastic modulus

- 38 -

(and therefore the rigidity) of the film. Films with low elastic moduli are unlikely to satisfy the requirements for favorable tablet preparation due to the associated elastic recovery which will occur immediately on the removal of the applied stress. Thus, it was concluded that films exhibiting a relatively high elastic modulus provide greatest protection to the millisphere core and coat on compression.

Elongation at break can be used as a measure of the mechanical properties of films. Lehmann et al (*Drug Made in Germany*, 37(2):53-60 (1994)) used this approach to measure the elongation at break of films formed from polymethacrylate dispersions. Films 8 x 10 cm, 150-200 μm thick were formed by layering 15 ml of the 30% aqueous dispersions or mixtures thereof on teflon coated glass plates, and drying 15 hrs at 40°C. The films were equilibrated at 50% relative humidity for 24 hrs at room temperature. Eudragit® NE 30 D, the aqueous dispersion of methylmethacrylate-ethylacrylate copolymer, did not need addition of plasticizer, and the film showed high elongation at break of approximately 600%. Eudragit® RL 30 D and RS 30 D, copolymers of methylmethacrylate, ethylacrylate and triethyl ammonioethyl methacrylate, used in sustained release, exhibit graded permeability and give films of sufficient flexibility after the addition of approximately 20% triethyl citrate plasticizer, when the elongation of break was above 75%. An elongation at break of 75% or more is sufficient for the compression of coated particles with or without very small damage of the release controlling membrane.

The study of the elongation at break of ethylcellulose has not been reported in the literature

because of the difficulty encountered in preparing the
free films. This is due to the excessive adhesiveness
to the casting surface, together with the brittleness
of ethylcellulose.

H.   Compaction of Tablets
The compaction of dry powders has been described
in numerous articles (Leuenberger et al, *Pharm. Res.*,
3:12-22 (1986); Hersey et al, *Nature*, 228:96 (1971);
Cole et al, *Pharm. Acta Helv.*, 50:28-32 (1975);
Hersey et al, *J. Pharm. Sci.*, 62:2060 (1981);
David et al, *J. Pharm. Sci.*, 66:155-159 (1977);
McKenna et al, *J. Pharm. Pharmacol.*, 34:347-351
(1981); Rees et al, *J. Pharm. Pharmacol.*, 30:601-607
(1978); Armstrong, *Int. J. Pharm.*, 49:1-13 (1989);
Turba et al, *Chem.-Ing.-tech.*, 36:230-240 (1964);
Rumpf, *Chem.-Ing.-tech.*, 46:1-11 (1974); and Shubert,
Chem.-Ing.-tech., 51:266-277 (1979)). It consists of
two stages: compression of the particulate solid and
bonding of the particles.

1.   Tablet Strength - Compression
Pressure Profiles
The simplest, and perhaps most universally used
means to study the compaction process involves the
relationship between punch force and tablet
"hardness". The term "hardness" has been used for
many years to describe the force required to break a
tablet when subjected to a diametral load. Since the
term "hardness" has a definite meaning in material
science, it is probably best to use terms, such as
"crushing strength" or "breaking strength" to describe
this parameter. Crushing strength, however, is not a
fundamental property of the compact. Tablet tensile

- 40 -

strength measured by diametral compression is more appropriate. If the tablet fails under tension by splitting cleanly into diametral halves, then its tensile strength (σ) can be calculated using the Equation (1) below (Fell et al, *J. Pharm. Sci.*, 59:688-691 (1970))

$$\sigma = \frac{2\ P}{\Pi\ Dt} \qquad \text{Equation (1)}$$

where P is the applied load, D is the tablet diameter, t is the tablet thickness. This equation applies only to cylindrical tablets and includes the following assumptions:

      (1)   The tablet is isotropic body;

      (2)   The tablet obeys Hooke's law; and

      (3)   The modules of elasticity in compression and tension are the same.

Despite the fact that none of the above-mentioned assumptions are currently met in pharmaceutical compacts, the use of this equation improves the reproducibility of the data, because the data is normalized with respect to tablet dimensions, since both diameter and thickness are included in the equation. Variations in the consolidation time (to maximum force), dwell time (at maximum force), contact time (time for compression and decompression excluding ejection), die resistance and ejection may give rise to changes in compaction mechanism and lamination, resulting in compacts with different strength characteristics (David et al, *supra*; Heistand et al, *J. Pharm. Sci.*, 66:510-519 (1977); and Schlanta et al, *J. Pharm. Sci.*, 53:562-564 (1970)).

2.   Changes in Bed Density
         During Compaction

        One of the effects of powder compaction is an
increase in the bulk density of the starting material.
Quite often, the relationship between the applied
pressure and density or porosity appears linear over
the normal tabletting range of the applied pressure.
Various empirical equations have been proposed to
characterize this relationship.   Perhaps the best
known and widely used the Heckel equation, i.e.,
Equation (2) below (*Trans. Metall. Soc. A.I.M.E.*,
<u>221</u>:671-675 (1961); and *Trans. Metall. Soc. A.I.M.E.*,
<u>221</u>:1001-1008 (1961)), which is based on the void
spaces decreasing as a first order process.

$$\ln \frac{1}{1-D} = KP + A \qquad \text{Equation (2)}$$

where D is the relative density of the compact at
pressure P, K is a material constant and is the slope
of the straight line portion of the plot.   <u>The
reciprocal of K is the mean yield pressure of the
material (P_y)</u>.   The term A is a function of the
original compact volume, and can be related to the
densification that occurs during die filling plus that
which occurs by particle rearrangement before any
appreciable interparticle bonding starts.

        Sheik-Salem et al (*J. Pharm. Pharmacol.*,
<u>33</u>:491-494 (1981)) noted that the Heckel equation is
not derived from theoretical considerations of the
compaction process, but is essentially a curve-fitting
equation that provides reasonable correlation with the
observed facts over a wide range of pressures,
especially in the regions of interest where a compact
is being formed.   Several authors have used the Heckel
equation to study the deformation mechanism of

- 42 -

materials (Hersey et al (1971), *supra*; Hersey et al (1981), *supra*; McKenna et al, *supra*; Rees et al, *supra*; Sheik-Salem et al, *supra*; Fell et al, *J. Pharm. Sci.*, 60:1866-1869 (1971); York et al, *J. Pharm. Pharmacol.*, 25:1P-11P (1973); de Boer et al, *Powder Technol.*, 20:75-82 (1978); Rue et al, *J. Pharm. Pharmacol.*, 30:642-642 (1978); York, *J. Pharm. Pharmacol.*, 31:244-246 (1979); Chowhan et al, *Int. J. Pharm.*, 5:139-148 (1980); Paronen et al, *J. Pharm. Pharmacol.*, 35:627-635 (1983); Duberg et al, *Powder Technol.*, 46:67-75 (1986); Marchall et al, *Int. J. Pharm.*, 67:59-68 (1991); and Hussain et al, *Int. J. Pharm.*, 70:103-109 (1991)). Hersey et al (1971), *supra*, used Heckel's plots to differentiate between plastic deformation and fragmentation. These authors classified Heckel plots into two types (Figures 3A and 3B). In type 1 behavior (Figure 3A), densification under pressure is due initially to particle rearrangement, and then subsequently to plastic deformation without any fragmentation; Heckel plots of different particle size fractions of a material are parallel. However, in type 2 behavior (Figure 3B), consolidation occurs largely by fragmentation. Thus, the initial structure of the material is progressively destroyed so that above a certain pressure, coincident linear relations are obtained for all size fractions.

Caution should be observed in interpreting the results of Heckel analysis since the numerical value for the yield pressure has been shown to be dependent on experimental conditions, such as punch diameter, compaction rate and method of measuring relative density (York (1979), *supra*). Rees et al, *supra*, examined the effect of different contact times under

compression on the relative density of tablets
utilizing the Heckel equation. They noticed that for
plastically deforming materials, such as MCC, tablet
density increased with an increase in contact time.
However, dicalcium phosphate, a brittle material,
showed no changes in density with contact time.
Roberts et al (*J. Pharm. Pharmacol.*, 37:377-384
(1985)) examined the effect of punch speed on the
compaction of a variety of materials using the Heckel
equation. For materials known to deform plastically,
there was an increase in yield pressure with punch
speed. This was attributed to either a change from
plastic to brittle behavior, or a reduction in the
amount of plastic deformation due to the time
dependent nature of plastic flow. For materials known
to consolidate by fragmentation, there was no change
in yield pressure with punch speed. Roberts et al
supra, also presented an equation, Equation (3) below,
to determine the strain rate sensitivity (SRS) of the
various materials tested.

$$SRS = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100 \qquad \text{Equation (3)}$$

where P_{y1} and P_{y2} are yield pressures at fast and slow
punch velocities, respectively. The materials which
were more strain rate sensitive were those which
deform plastically. Thus, Roberts et al, *supra*
provided a quantitative measure of the strain rate
sensitivity of materials.

3. Critical Aspects in the
Compaction of Beads

Compaction of sustained release tablets
containing coated pellets is becoming increasingly
important. When such a dosage form is developed, the

- 44 -

coated pellets must withstand the process of compaction without being damaged in order to prevent any undesirable effects on the biologically active ingredient release properties. The type and amount of coating agent, the size of the subunit, the selection of external additives having a cushioning effect, and the rate and magnitude of the applied pressure must be carefully considered (Çelik et al, *Drug Dev. Ind. Pharm.*, 20(20):3151-3173 (1994)).

The process of millisphere compaction involves the application of stress to polymer-coated spherical cores. In order to fully understand the interrelationships between the mechanical properties of the film, the millispheres and the resulting compacts, it is necessary not only to evaluate and quantify the mechanical properties of the polymers as free-films, but also to study the properties of the polymeric membrane *in situ* on the millisphere core. The desirable mechanical properties of coated millispheres to be compacted into a tablet together with excipients or placebo cushioning beads should be such that they are strong, not brittle and have low elastic resilience. It is important in this dosage form that the millispheres and their coatings remain undamaged and intact so that the release profile of the biologically active ingredient is not changed.

The mechanical properties of both uncoated and coated ibuprofen containing millispheres was investigated by Aulton et al, *supra*, using a single particle crushing assembly in which the force required to cause single millisphere fracture and particle displacement under an applied load is recorded. The generation of this information facilitated estimation of the tensile stress and elastic modulus for each

millisphere formulation studied. These properties were related to the fundamental bonding forces arising from the pelletization process, which determine the strength of the millisphere, and to the contribution made to the overall mechanical properties of the millispheres by the presence of the film coating (and thus, in turn, its mechanical properties) The presence of a film coat applied by means of an aqueous polymeric dispersion of polymethacrylates also influenced the crushing strength and the elastic properties of ibuprofen millispheres. Increasing the polymer loading has the effect of increasing the crushing strength of millispheres, whilst simultaneously enhancing millisphere resilience (characterized by a reduction in the elastic modulus).

Maganti et al (*Int. J. Pharm.*, 95:29-42 (1993)) observed significant changes between the compaction properties of the powder and pellet forms of the same formulations. In their study, the powder formulations deformed plastically and produced stronger compacts, whereas their pellet forms exhibited elastic deformation and brittle fragmentation, which resulted in compacts of lower tensile strength. They reported that the addition of Surelease® as a coating material altered the deformation characteristics of uncoated pellets by introducing plasto-elastic properties into their previously brittle and elastic nature.

Juslin et al (*Pharm. Ind.*, 42:829-832 (1980)), in their study of the feasibility of achieving controlled release of a biologically active ingredient from compacts of coated spheres, observed that the biologically active ingredient release rate from phenazone spheres, coated with acrylates polymers mixed with different additives, increased with an

- 46 -

initial increase in the applied pressure. This was attributed to the cracks in the coat that formed during compaction. However, the authors claimed that further increases in pressure again retarded the release profile, possibly due to closer interparticulate contacts within the tablet, which partly compensated for the leaks of the pellet coats.

Badwan et al (*Drug Dev. Ind. Pharm.*, 11:239-256 (1985)) reported an increase in the drug release profile of sulphamethamethoxazole beads when compacted into a tablet.

Bobmeier et al (*J. Pharm. Sci.*, 78:819-822 (1989)) compacted biodegradable spheres prepared from polylactides. They observed that the energy imparted during compaction caused fusion of the low molecular weight polylactide particles, resulting in transparent pellets with no visible particle boundaries.

Béchard et al (*Drug Dev. Ind. Pharm.*, 18:1927-1944 (1992)), in their investigations of the effect of compaction on biologically active ingredient release from compacts of varying mesh cuts of Aquacoat® coated microspheres containing chlorpheneramine maleate, reported massive film fracture occurring at high pressures, regardless of the microsphere particle size and external additives used.

Lehmann et al, *supra*, coated small particles such as crystals, granules and pellets of particle size in the range of 0.3-1.2 mm with aqueous dispersions of methacrylic acid and methacrylic ester copolymers for taste masking, resistance to gastric fluid and diffusion controlled sustained release properties, and compressed them into fast disintegrating tablets. An admixture of 25-50% of tabletting excipients as

fillers and disintegrants was necessary. Some damage
of the coatings were observed with some brittle
coating polymers of polymethacrylates. More flexible
films (having an elongation at break of more than 75%)
5   were able to withstand the mechanical stress of
compression so that the release pattern of the
disintegrating tablet was very similar or nearly the
same as the uncompressed particles. Examples were
given for taste masking of paracetamol, sustained
10 release preparation of potassium chloride and
theophylline, and also enteric coated acetylsalicylic
acid and indomethacin.

The Haubitz et al (*Drugs in Germany*, 38(4) (1995))
produced theophylline-containing multiple units
15 tablets with a pellet amount of 70% in MCC as a filler
binder, crosslinked polyvinylpyrrolidone as a
disintegrant and Aerosil® as a glidant. The pellets
were produced by powder-layering theophylline in a
Eudragit® NE 30 D matrix onto sugar spheres, followed
20 by coating with an additional release controlling
barrier. A decrease in the release of theophylline
from compacted beads, was observed relative to
uncompacted beads, and was attributed to delayed
tablet disintegration and the reduction in the number
25 of pores of the pressed pellets caused by local
melting processes of the affected coat area with
subsequent closing of the pores.

The selection of external additives is also of
importance in the design of multiunit tablets since
30 these additives are expected to prevent the occurrence
of film cracking in the coated subunits. Their
compactibility with the pellets, in terms of particle
size, is also very critical, since a non-uniform size
distribution can cause segregation, resulting in
35 tabletting problems, such as, weight variation, poor

- 48 -

content uniformity, etc. In order to minimize the occurrence of problems due to a non-uniform size distribution, placebo microspheres, with good "compaction" and "cushioning" properties, can also be used as diluents if the size of the active beads is much larger than that of the external powder additives. Another alternative would be to produce pellets of smaller sizes. Small-size biologically active ingredient-loaded pellets also improve the content uniformity of low dose biologically active ingredients. However, the surface area to be coated will increase as the size of the pellets decreases.

4. Use of Inert "Cushioning" Beads as Diluents

Good blending and minimal segregation is essential in order to achieve satisfactory uniformity of weight and content of the tablet dosage form. The potential problem of segregation in any particulate system must be addressed. It is influenced by factors, such as markedly differing particle size, density or shape. In order that the occurrence of segregation between the biologically active ingredient-loaded pellets and excipient particle is minimized, it is deemed necessary to choose large particle size excipients. This could be achieved by the preparation of inert beads of the same size and approximately the same density. The inert cushioning beads should be mechanically weaker than the coated biologically active ingredient-loaded ones.

Millili et al, *supra*, reported that the strength and physical properties of beads containing MCC were affected by the granulating solvent. In their work, water granulated MCC beads were found to be stronger, hard, and uniform in shape, whereas the

95/5 ethanol/water granulating solvent resulted in
beads with lower strength and less uniform shape. On
the other hand, the former beads exhibited poorer
compressibility than the latter ones. This was
attributed to the weak bonding of the 95% ethanol
granulated pellets which ruptured upon compaction,
exposing more smooth surface to surface contacts for
bonding. The water granulated beads resisted
rupturing due to their high bond strength, and allowed
less surface-to-surface contacts for bonding to occur,
thus producing weaker tablets.

Aulton et al, *supra*, tried to use different
approaches to produce inert "cushioning" beads for
cushioning of coated biologically active
ingredient-loaded sustained action millispheres in
order to prevent segregation due to size or density.
Inert beads containing high MCC levels, by virtue of
the inherent bonding capacity of this material, were
exceedingly hard. In addition, inert beads containing
high lactose levels were also very hard. This results
from the partial dissolution of lactose during wet
massing and extrusion, and the formation of solid
bridges during drying. It was thought that the
replacement of all or part of the granulating water
with isopropyl alcohol (in which lactose was
insoluble) might enable the preparation of softer
inert cushioning beads which would readily fragment at
low pressure during tabletting. This was not the
case: the resulting beads were still too strong and
required three times greater applied force than that
of the biologically active ingredient-loaded beads
before they crush. Thus, it was concluded that the
admixture of biologically active ingredient-loaded
beads and inert beads was not a viable proposition.

- 50 -

An attempt was made to mix the biologically active ingredient-loaded beads with large particle size excipients. Avicel® PH200 (200 μm average size) and Meggle Lactose EP grade D10 (coarse-crystalline) with a mean size equal to 800 μm at an optimized diluent blend of lactose 19.5%, MCC 20% (PH200) and magnesium stearate 0.5%, were chosen. The rest of the tablet contained biologically active ingredient-loaded beads. The uniformity of content of the biologically active ingredient was 4.22% (relative standard deviation) under the pilot-scale conditions utilized. It is accepted however, that this might not be the case on scaling-up the process.

In summary, the formulation of ready-made suspensions containing controlled release beads have been associated with premature leaching of the biologically active ingredient. The use of a dispersible tablet to form an instantaneous suspension can circumvent this problem together with the possibility of administering large doses of biologically active ingredients. The ideal tablet to form an instantaneous sustained release suspension should disintegrate quickly in water (less than 5 sec) followed by the formation of a viscous suspension (within 1-2 min) to delay the settling of the biologically active ingredient-loaded membrane-coated beads until the dose is swallowed by the patient. In order to formulate this tablet three components are needed:

    (1)   Biologically active ingredient-loaded membrane-coated beads intended to deliver the dose over a long period of time;

    (2)   A viscosity enhancer capable of delaying the sedimentation of the

biologically active ingredient-loaded
beads; and

(3)   A filler system capable of producing
mechanically strong compacts while
5   protecting the biologically active
ingredient-loaded beads from
fracturing.

Figure 4 is a flow chart depicting the systematic
approach used in the formulation of this dosage form.

10   III. Statement of the Problem

When large doses of biologically active
ingredients are required, large tablets and capsules
are not a viable option, since they are difficult to
swallow, resulting in impaired patient compliance,
15   especially among pediatric and geriatric patient
populations. Liquid oral suspensions can be used to
deliver large doses of biologically active
ingredients. However, the incorporation of
controlled-release particles into aqueous vehicles
20   often results in premature loss of the biologically
active ingredient during storage. The formulation of
a special solid oral dosage form which can
disintegrate rapidly in water to form an instantaneous
homogenous suspension can be used to administer large
25   dosages of biologically active ingredients. It
eliminates the physical problems of biologically
active ingredient leaching from sustained-release
coated beads, as well as providing improved packaging
and transportation properties, and a ready measured
30   dose. To formulate such a dosage form, a rapidly
disintegrating tablet capable of forming a viscous
suspension is needed. The development of a viscous
gel should follow the disintegration of the tablet
otherwise, tablet disintegration would be prevented.

- 52 -

A swellable material capable of generating viscosity when coming in contact with water is needed together with a biologically active ingredient for immediate or sustained release delivery, and a filler system which possesses certain properties, among which are compactibility and the capability to disintegrate quickly.

Biologically active ingredient-loaded membrane-coated beads, when compacted to form a tablet, will fracture due to the applied force resulting in cracking of the membrane and subsequent failure of the delivery system. Mixing and compressing the biologically active ingredient-loaded beads with highly compressible fillers can minimize this damage. However, size differences between the fillers and the biologically active ingredient-loaded beads might result in segregation with consequent content uniformity and weight variation problems. The production of cushioning beads which deform at lower pressures during tabletting to prevent the fracture of the membrane-coated biologically active ingredient-loaded beads is needed to minimize the segregation propensity. The viscosity enhancer, biologically active ingredient-loaded membrane-coated beads and cushioning filler beads need to be mixed and compacted to form a tablet which can disintegrate quickly in water to form a homogenous suspension.

IV. Hypotheses

It was hypothesized in the present invention that the incorporation of the viscosity enhancer in separate entities, such as layering onto placebo or biologically active ingredient-loaded beads, or extrusion-spheronization to form beads might circumvent the problem of prolonged tablet

- 53 -

disintegration. The incorporation of the viscosity enhancer as fine powder in a tablet matrix could prevent the rapid disintegration and subsequent dispersion of the contents of the tablet. It is believed that fine powder of the viscosity enhancer tend to network with each other, so that on contact with water, the networked polymer particles at the surface would hydrate, preventing the further penetration of water to the interior of the tablet, and the disintegration process would be inhibited.

It was also hypothesized in the present invention that freeze-drying of MCC pellets produced by extrusion-spheronization would improve compactibility over other drying techniques. The incorporation of materials which can increase the water uptake by the extrudate is also hypothesized in the present invention to improve the porosity and compactibility of the freeze-dried beads. MCC can be processed so that the size of the filler particles is equal to the size of the biologically active ingredient-loaded beads to minimize the segregation propensity.

It was also hypothesized in the present invention that a difference in the particle size of the filler would result in weight variation and content uniformity problems. A difference in the particle size between filler-binder and biologically active ingredient-loaded beads tend to cause segregation as manifested in weight variation and content uniformity.

It was also hypothesized in the present invention that unlike ethylcellulose films, which are very brittle, polymethacrylate films can withstand the stresses of compaction with minimal fracturing and slight change in the biologically active ingredient release kinetics. The type of membrane-coating applied to the biologically active ingredient-loaded

- 54 -

beads is important in determining the ability of the coated beads to handle the mechanical stresses of the compaction.

It was also hypothesized in the present invention that a tablet composed of biologically active ingredient-loaded membrane-coated beads, processed viscosity enhancer and a filler system which disintegrate quickly in water to form an extemporaneous uniform suspension can be produced to provide a new delivery system to deliver sustained-released biologically active ingredients in the form of suspension to pediatric and geriatric patients.

SUMMARY OF THE INVENTION

An object of the present invention is to provide highly porous and compactible cushioning beads, and which are useful for tabletting with biologically active ingredient-loaded beads.

Another object of the present invention is to provide water-dispersible tablets having high tensile strength.

Still another object of the present invention is to provide tablets containing beads which give rise to sustained delivery of a biologically active ingredient

Yet another object of the present invention is to provide tablets containing a swellable material able to rapidly generate viscosity when coming in contact with water.

An additional object of the present invention is to provide tablets which disintegrate rapidly in water, and form a homogenous suspension which can be easily swallowed by children and the elderly, with minimal effect on the biologically active ingredient release properties.

A further object of the present invention is to provide tablets which disintegrate rapidly in water, and form a homogenous suspension when large doses of biologically active ingredient are needed, but where swallowing of a large tablet or capsule poses a problem.

These and other objects of the present invention, which will be apparent from the detailed description of the invention provided hereinafter, have been met, in one embodiment, by a cushioning bead comprising microcrystalline cellulose, wherein said cushioning bead is prepared by extrusion-spheronization, followed by freeze-drying.

In another embodiment, the above-described objects of the present invention have been met by a tablet comprising:

(i)   biologically active ingredient-loaded beads; and

(ii)   cushioning beads comprising microcrystalline cellulose, wherein said cushioning beads are prepared by extrusion-spheronization, followed by freeze-drying.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict the molecular structure of carbomer resin in the partially solvated state (Fig. 1A), and the fully solvated state (Fig. 1B).

Figure 2 shows a schematic diagram of an aeromatic rotoprocesser.

Figures 3A and 3B show Athy-Heckel plots for different deformation mechanisms type 1 (Fig. 3A) and type 2 (Fig. 3B).

- 56 -

Figure 4 is a flow chart depicting the formulation and manufacturing of tablets for instantaneous sustained release suspension.

Figure 5 shows viscosity of different concentrations of carbomer EX214 solutions as a function of shear rate.

Figure 6 shows viscosity of different concentration of Visquick® 11 solutions as a function of shear rate.

Figure 7 shows viscosity of different concentrations of Visquick® 21 solutions as function of shear rate.

Figure 8 shows viscosity of different concentrations of Insta*Thick Xanthan® solutions as a function of shear rate.

Figure 9 shows viscosity of various polymers at concentrations suitable to be incorporated in self-disintegrating tablets as a function of shear rate.

Figure 10 shows release of carbomer EX214 as a function of time from powder-layered beads using different alcoholic PVP solutions.

Figure 11 shows the effect of croscarmellose sodium incorporation on the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization.

Figure 12 shows the effect of crospovidone incorporation on the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization.

Figure 13 shows the effect of MCC/mannitol ratio on the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization.

- 57 -

Figure 14 shows the release of carbomer EX214 as a function of time from duplicate batches of beads produced by extrusion-spheronization.

Figure 15 shows the effect of sphere size on the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization.

Figure 16 shows the effect of alcohol/water ratio on the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization,

Figure 17 shows the release of carbomer EX214 as a function of time from beads produced by extrusion-spheronization and powder-layering.

Figure 18 shows the effect of croscarmellose sodium on the compactibility of freeze-dried MCC beads.

Figure 19 shows the effect of croscarmellose sodium on the compactibility of freeze-dried MCC:lactose (25:75) beads.

Figure 20 shows the effect of MCC:lactose ratio on the compactibility of freeze-dried beads containing 0% croscarmellose sodium.

Figure 21 shows the effect of MCC:lactose ratio on the compactibility of freeze-dried beads containing 8.0% croscarmellose sodium.

Figure 22 shows the compactibility of freeze-dried replicate formulation containing 4.0% croscarmellose sodium in MCC:lactose (62.5:37.5).

Figure 23 shows the effect of crospovidone on the compactibility of freeze-dried MCC beads.

Figure 24 shows the effect of sodium starch glycolate on the compactibility of freeze-dried MCC beads.

Figure 25 shows the effect of incorporation of different superdisintegrants at a 8.0% level on the compactibility of freeze-dried MCC beads.

Figure 26 shows the effect of different croscarmellose and MCC:lactose ratios on the compactibiity of freeze-dried beads.

Figure 27 shows the effect of different superdisintegrants on the compactibility of freeze-dried MCC beads.

Figure 28 shows Athy-Heckel plots of freeze-dried beads containing different levels of croscarmellose sodium in MCC.

Figure 29 shows Athy-Heckel plots of freeze-dried beads containing different levels of croscarmellose sodium in MCC:lactose (25:75).

Figure 30 shows Athy-Heckel plots of tray-dried and freeze-dried beads containing plain MCC.

Figure 31 shows Athy-Heckel plots of tray-dried and freeze-dried beads containing 8.0% croscarmellose sodium in MCC.

Figure 32 shows Athy-Heckel plots of freeze-dried beads containing 8.0% croscarmellose sodium in formulations having different MCC:lactose ratio.

Figure 33 shows compaction profiles of propranolol hydrochloride beads in different filler systems.

Figure 34 shows compaction profiles of phenylpropanolamine hydrochloride beads in different filler systems.

Figure 35 shows compaction profiles of theophylline RD010 beads in different filler systems.

Figure 36 shows compaction profile of 12.5% theophylline RD011 beads in cushioning beads.

Figure 37 shows the dissolution of propranolol hydrochloride from uncompacted and compacted beads (25% propranolol beads/75% cushioning beads).

Figure 38 shows the dissolution of propranolol hydrochloride from uncompacted and compacted beads (50% propranolol beads/50% cushioning beads).

Figure 39 shows the dissolution of phenylpropanololamine hydrochloride from uncompacted and compacted beads (12.5% PPA-HCl beads/87.5% cushioning beads).

Figure 40 shows the dissolution of phenylpropanolamine hydrochloride from uncompacted and compacted beads (25% PPA-HCl beads/75% cushioning beads).

Figure 41 shows the dissolution of propranolol hydrochloride from uncompacted and compacted beads (Effect of bead load at a compression pressure of approximately 240 Kg/cm^2).

Figure 42 shows the dissolution of phenylpropanolamine hydrochloride from uncompacted and compacted beads (Effect of bead load at a compression pressure of 168.9 Kg/cm^2).

Figure 43 shows the dissolution of propranolol hydrochloride from uncompacted and compacted beads (25% propranolol beads/75% MCC).

Figure 44 shows the dissolution of phenylpropanolamine hydrochloride from uncompacted and compacted beads (12.5% PPA-HCl beads/87.5% MCC).

Figure 45 shows the dissolution of propranolol hydrochloride from uncompacted and compacted beads (Effect of cushioning beads versus MCC).

Figure 46 shows the dissolution of phenylpropanolamine hydrochloride from uncompacted and compacted beads (Effect of cushioning beads versus MCC).

Figure 47 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010

- 60 -

beads (12.5% theophylline RD010 beads/87.5% cushioning beads).

Figure 48 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (25% theophylline RD010 beads/75% cushioning beads).

Figure 49 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (Effect of bead load at a compression pressure of 331.8 Kg/cm^2).

Figure 50 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (25% theophylline RD010 beads/75% MCC).

Figure 51 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (Effect of cushioning beads versus MCC at a compression pressure of 331.8 Kg/cm^2).

Figure 52 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (Effect of cushioning beads versus MCC at a compression pressure of 603.1 Kg/cm^2).

Figure 53 shows the dissolution of theophylline from uncompacted and compacted theophylline RD011 beads (12.5% theophylline RD011 beads/87.5% cushioning beads).

Figure 54 shows the compaction profile of theophylline RD010 beads in cushioning beads and carbomer beads.

Figure 55 shows the dissolution of theophylline from uncompacted and compacted theophylline RD010 beads (8.3% theophylline RD010 beads, 16.7% carbomer beads and 75% cushioning beads).

- 61 -

DETAILED DESCRIPTION OF THE INVENTION

As discussed above, in one embodiment, the above-described objects of the present invention have been met by a cushioning bead comprising microcrystalline cellulose, wherein said cushioning bead is prepared by extrusion-spheronization, followed by freeze-drying.

Extrusion-spheronization is a well-known process (U.S. Patent 3,277,520; Conine et al, *Drug Cosmet. Ind.*, April:38-41 (1970); and Reynolds et al, *Che. Aerosol News*, 41:40-43 (1970)).

Spheronizers are well-known in the art, and are commercially available from Niro-Aeromatic, Inc. Caleva, LUWA (Fuji Paudal), Machine Collete, Glatt Air Techniques and Patterson Kelley. A spheronizers is a device consisting of a vertical hollow cylinder (bowl) with a horizontal rotating disc (friction plate) located inside. Extrudate is charged onto the rotating plate and broken into short segments by contact with the friction plate, by collision between particles, and by collisions with the wall. Mechanical energy introduced by the spinning friction plate is transmitted into kinetic energy in the form of a "mechanically fluidized bed", a more-or-less random mixture of air-borne particles moving at high velocities. Further processing will cause the extrudate to deform gradually into a spherical shape.

Beads (or pellets) are distinguishable from granules. Pelletization is an agglomeration process that converts fine powders or granules of, e.g., bulk biologically active ingredient and/or excipient into small, free-flowing, spherical or semi-spherical units. As opposed to the process of granulation, the production of beads results in a narrow size-range

- 62 -

distribution. The more spherical nature of the beads
compared to granules provides better flow, and reduces
segregation due to shape differences. Also, the good
surface morphology of beads provides an optimal
surface for applying a functional coating, when
desired.

In the present invention,
extrusion-spheronization is carried out by the method
comprising the steps of:

    (a) granulating the microcrystalline
        cellulose; and

    (b) extruding the resulting
        granulation obtained in step (a)
        onto a spheronizer.

Microcrystalline cellulose is well-known in the
art, and is available from a variety of commercial
sources, e.g., Avicel® (FMC), Emococel® (Mendell) and
Vivocel® (JRS).

The amount of microcrystalline cellulose employed
is not critical to the present invention, and depends
upon the desired density, porosity, and compactibility
of the final freeze-dried cushioning beads.
Generally, the amount of microcrystalline cellulose
employed is about 20-100%, preferably about 60-95%.

In a preferred embodiment, the cushioning beads
also comprise a disintegrant. The particular
disintegrant employed is not critical to the present
invention. Examples of such disintegrants include
croscarmellose sodium, sodium starch glycolate,
crospovidone, starch, and pregelatinized starch.
Croscarmellose sodium is the preferred disintegrant
employed in the present invention.

Croscarmellose sodium is also well-known in the
art, and is available from a variety of commercial

- 63 -

sources, e.g., Ac-Di-Sol® (FMC) and Primellose® (AVEBE).

The amount of disintegrant employed is also not critical to the present invention, and depends upon the desired density, porosity, and compactibility of the freeze-dried cushioning beads. Generally, the amount of disintegrant employed is about 0-50%, preferably about 5.0-40%.

The weight ratio of microcrystalline cellulose to disintegrant employed is also not critical to the present invention, and depends upon the desired density, porosity, and compactibility of the final freeze-dried cushioning beads. Generally, the weight ratio of microcrystalline cellulose to disintegrant employed is about 1:0-0.2:0.8, preferably about 0.95:0.05-0.6:0.4.

The desired density (granular density) is generally in the range of 0.5-1.5 g/ml, and is preferably identical to that of the biologically active ingredient-loaded beads.

The desired porosity is generally in the range of 30-80%, preferably 50-70%.

The desired compactibility is that which upon compaction of the cushioning beads produces a tablet with a friability of not more than about 1.0%.

Microcrystalline cellulose (as well as the disintegrant) are powdery components, and are granulated in step (a) with water as the granulating agent. The water may be a hydroalcoholic solution containing an alcohol, such as ethyl alcohol or propyl alcohol. The amount of water (hydroalcoholic solution) used will affect the mechanical properties of the freeze-dried beads, including the porosity, density, and compactibility. The amount of water (hydroalcoholic solution) employed depends on the

- 64 -

composition of the powder mixture used in step (a).
Generally, the amount of water (hydroalcoholic
solution) used is such to give a final concentration,
for solids in the granulation extruded in step (b), of
about 20-80% (w/v).

The cushioning beads can, in addition, contain
water-soluble fillers, such as lactose and sorbitol,
or other water-insoluble fillers, e.g., dibasic
calcium phosphate. These components can be
co-granulated with the microcrystalline cellulose and
disintegrant in step (a).

The amount of filler (either water-soluble or
water-insoluble) present in the cushioning beads is
not critical to the present invention and depends upon
the desired density, porosity and compactibility.
Generally, the amount of filler (either water-soluble
or water-insoluble) employed in the range of about
0-80%, preferably about 0-50%.

It was found in the present invention that there
is a statistically significant interaction between
croscarmellose sodium and MCC/lactose ratio on the
tensile strength of the compacts. Increasing the
percentage of croscarmellose sodium in the formulation
predominantly containing MCC produces compacts with
higher tensile strength than if such an increase
occurred in a lactose-predominant formulation. As the
concentration of croscarmellose sodium is increased to
8.0%, an increase in the MCC/lactose ratio produces
tablets with higher tensile strengths. In the
presence of 8.0% croscarmellose sodium in MCC, the
high porosity associated with the high granulation
fluid requirement results in softer beads, which
readily deform upon the application of pressure to
give hard tablets. In formulations dominated by
lactose, the presence of 8.0% croscarmellose sodium

increases the water requirement and porosity to a lesser extent, but these beads were still hard due to solid bridge formation.

The cushioning beads can also contain other additives, such as colorants (e.g., FD&C and D&C, and their lake forms); sweeteners (e.g., various sugars, such as sucrose, mannitol, saccharin and its salts, and aspartame); flavoring agents (e.g., Anathenole N.F., Benzaldehyde N.F., Vanillin N.F., Ethyl vanillin N.F., Ethyl acetate N.F., and Methyl salicylate N.F.); and buffering agents, as is conventionally employed in the art.

The pressure at which the granulation in step (b) is extruded is not critical to the present invention, and depends upon the composition of the granulation to be extruded, its initial moisture content, the rotation speed of the spheronizer, the configuration of the extrusion blade and shaft, and the aperture size and shape of the extrusion screen of the spheronizer.

The rotation speed of the spheronizer is not critical to the present invention, and depends upon the water content of the extrudate, the composition and characteristics of the extrudate, the size and texture of the friction plate, and the spheronizer residence time. Generally, the friction plate is rotated at a speed of about 200-1500 RPM, preferably about 400-700 RPM.

The shaft and blade design varies in accordance with how much compression is needed. A low pressure extruder may have regularly spaced screw flights which will give some compression, but the main function of the flights is to transport the material down the barrel of the extruder. Another design utilizes

- 66 -

progressively closer screw flights, a decreasing helix
angle, to develop very high compressive forces.

The aperture size of the extruder screen of the
spheronizer is not critical to the present invention,
and depends upon the desired size of the beads to be
produced.   Generally, the aperture size of the
extruder screen ranges from about 0.2-2.0 mm,
preferably about 0.5-1.5 mm.

The shape of the aperture is generally
cylindrical, although it can have a tapered inlet or
outlet, or have a conical shape.

The friction plate of the spheronizer may have
variety of sizes and textures. The size of the
friction plate is not critical to the present
invention. Generally, the size of the friction plate
ranges from about 230-1000 mm, and affects the working
capacity of the spheronizer (0.25-1.5 to 25-60 liters,
respectively). The friction plate generally will have
a cross-hatch pattern where the grooves intersect each
other at 90° angles. A possible more efficient
pattern is a radial design plate, where grooves
emanate from the center like spokes of a bicycle
wheel.   In this case, more cutting edges are
perpendicular to the direction of rotation so the
resulting transfer of energy is greater. The grid
pattern is usually matched with the desired particle
size.   For example, a 1.0 mm granule would be
processed on a friction plate with an opening (groove)
that is 50-100% larger. The wider groove allows the
extrudate to fall into the openings so that the
leading edge of the peak will fracture with extrudate
into uniform lengths.

The spheronizer residence time is not critical to
the present invention, and depends upon the amount and
composition of the material added, the desired shape

and the degree of spheronization accomplished.
Generally, the spheronizer residence time is about
2.0-20 min, preferably about 4.0-8.0 min.

The temperature at which extrusion is carried out
is not critical to the present invention, and depends
upon the extrusion pressure. Generally, extrusion is
carried out at about 10-30°C, preferably about
20-25°C.

Freeze-drying in step (b) is generally carried
out at temperatures below the freezing point or
collapse temperature. This is accomplished by keeping
the pressure in the system at a pressure that is below
the freezing point of the product. Freeze-drying
produces highly porous and compactible cushioning
beads, since the removal of water in the frozen state
leaves a skeleton of solid material. Evaporation of
water by other drying techniques, such as tray-drying
or fluid-bed drying is accompanied by disadvantageous
shrinking, which results in highly dense, and less
compactible beads.

As discussed above, in another embodiment, the
above-described objects of the present invention have
been met by a tablet comprising:

    (i)   b i o l o g i c a l l y   a c t i v e
        ingredient-loaded beads; and

  (ii) cushioning   beads comprising
        microcrystalline cellulose (and
        optionally   a   disintegrant),
        wherein said cushioning beads are
        p r e p a r e d   b y
        e x t r u s i o n - s p h e r o n i z a t i o n ,
        followed by freeze-drying.

The means for preparing the biologically active
ingredient-loaded beads is not critical to the present
invention. For example, the biologically active

- 68 -

ingredient-loaded beads can be prepared by techniques well-known in the art such as, extrusion-spheronization, solution/suspension layering, powder layering, balling (a pelletization process in which finely divided particles are converted, upon the addition of appropriate quantities of liquid, to spherical particles by continuous rolling or tumbling action), or fluidized bed roto-granulation.

The particular biologically active ingredient employed is not critical to the present invention, and may be any substance which is suitable for peroral administration, although the present invention is not limited to the use of substances which are only suitable for peroral administration.

Examples of such biologically active ingredients include pharmaceuticals, pesticides and herbicides.

The particular pharmaceutical employed is not critical to the present invention. Examples of such pharmaceuticals include potassium chloride (administered in hypokalemia); lithium salts (administered in psychotherapy); nonsteroidal anti-inflammatory drugs, such as ibuprofen; calcium salts (administered in the therapy of hypocalcemic states or for calcium supplementation); sodium fluoride (administered in the treatment of osteoporosis); pridinol or a salt thereof (administered as a muscle relaxant); dimethindine or a salt thereof (administered as an antihistaminicum); methyl-xanthines, such as propoxyphylline, dipropylline and/or theophylline (administered as bronchodilators); $O-\beta$-hydroxymethyl-rutoside (administered in the treatment of venous diseases); butamirate or a salt thereof, codeine or a derivative thereof, or noscapine (administered as antitussive

- 69 -

drugs); acetaminophen (administered as an antipyretic); vitamins or multivitamin preparations; β-blockers (administered as cardiovascular and vascular drugs); pyrisuccideanol, ticlopidine, dipyridamole or diazepam (administered against elderly or pediatric diseases); drugs used to balance hydroelectrolytes, such as for the treatment of diarrhoea; and erythromycin or a salt thereof or doxycycline or a salt thereof (administered as antibiotics).

The particular pesticide employed is not critical to the present invention. Examples of such pesticides include clomazone (Command®), sulfentrazone (Authority®) and clomazone/trifluralin (Commence®).

The particular herbicide employed is not critical to the present invention. Examples of such herbicides include zeta cypermephrin (Fury®), cadusafos (Rigby®) and bifenthrin (Brigade®).

Optionally, a coating material may be applied to the biologically active ingredient-loaded beads for controlling or sustaining the release properties of the biologically active ingredient, for taste masking, or for imparting resistance to gastric fluid.

The particular coating material employed is not critical to the present invention, and depends upon the purpose of the coating material, e.g., the desired release profile, the ability of the coating layer to stay intact, and the ability of the coating layer to withstand the mechanical stress of compaction without cracking.

Examples of coating materials useful for controlling or sustaining the release properties of the biologically active ingredient include methylcellulose, hydroxypropyl cellulose, ethylcellulose or latex derivatives thereof, such as

- 70 -

Surelease® and Aquacoat®, and methylacrylate ester
copolymers, such as Eudragit® RL 30D, RS 30D, L30
D-55, and NE30D.

Examples of coating materials useful for taste
masking include the above-listed materials useful for
controlling or sustaining the release properties of
the biologically active ingredient.

Examples of coating materials useful for
imparting resistance to gastric fluid include shellac,
cellulose acetate phthalate (Aquateric®), cellulose
acetate trimelliate, hydroxypropyl methylcellulose
phthalate, polyvinyl acetate phthalate (Coateric®),
hydroxypropyl methylcellulose acetate succinate
(AQOAT®), and methacrylic acid copolymers, such as
Eudragit® L30D and L100-55.

The thickness of the coating layer employed is
not critical to the present invention, and depends
upon the desired release profile of the biologically
active ingredient. Generally, the thickness of the
coating layer will be in the nano to micro ranges.

Alternatively, the above-listed materials (or
polymers) can be incorporated in a matrix system
together with the biologically active
ingredient-loaded beads to, e.g., sustain its action.
Such incorporation can be carried out during dry
powder mixing prior to granulation, or in the
granulation solution prior to
extrusion-spheronization, or in the other techniques
conventionally used to produce pellets or beads.

When incorporated into the matrix system, the
amount of such materials (or polymers) employed is not
critical to the present invention, and depends upon
the purpose of the material, e.g., the desired release
profile of the biologically active ingredient.

- 71 -

The tablets can also contain a viscosity enhancer. The particular viscosity enhancer employed is not critical to the present invention. Examples of such viscosity enhancers include carbomers, xanthan gum, guar gum, alginates, dextran, pectins, pregelatinized starches, polysaccharides, cellulose derivatives, such as sodium or calcium carboxymethylcellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose. Carboxymethylene (carbomer) is the preferred viscosity enhancer because such is effective at very low concentrations (0.1-0.3% (w/w), and has a quick hydration rate.

The viscosity enhancer may be present as individual beads, or may be a component of the biologically active ingredient loaded-beads, if those beads are intended for immediate delivery of the biologically active ingredient, i.e., where no sustained action or coating material (or polymer) is employed. In this case, the amount of viscosity enhancer employed in the biologically active ingredient-loaded beads is not critical to the present invention.

The viscosity enhancer beads may be produced by extrusion-spheronization using a hydroalcoholic solution, or by powder-layering alone, or together with the biologically active ingredient. This approach avoids the detrimental effects of ionic salts or pH modifiers on the ability of the viscosity enhancer to build-up viscosity when hydrated. Also, extrusion-spheronization of the viscosity enhancer using a hydroalcoholic granulating liquid reduces the tackiness thereof.

The particular hydroalcoholic solution employed is not critical to the present invention. Examples of such hydroalcoholic solutions employed include ethyl

- 72 -

alcohol, propyl alcohol, or a mixture thereof. The
alcohols may be mixed with water to provide the
hydroalcoholic solution.

The amount of alcohol in the hydroalcoholic
solution employed is not critical to the present
invention, and depends upon the viscosity enhancer
employed, and the processability (in terms of
tackiness) of the granulation and its extrudate.
Generally, the amount of alcohol will be about 0-100%,
preferably about 40-60%.

The size of the beads, whether they are the
cushioning beads, biologically active ingredient
loaded-beads or the viscosity enhancer beads, is not
critical to the present invention, but a similar size
and size distribution is required to minimize
segregation. Larger beads tend to float at or near
the top of the pellet mass prior to mixing in a
hopper, or the feeding frame during tabletting,
thereby severely altering the uniformity of the pellet
blend, and causing variability in the biologically
active ingredient content or potency of the tablet.
Generally, the beads have an average diameter of about
0.2-2.0 mm, preferably about 0.5-1.5 mm. The
biologically active ingredient-loaded beads generally
should be smaller than approximately 2.0 mm, so that
such can be transported continuously, together with
the food content, through the digestive tract. In
this manner, the quality, amount of timing of food
uptake, as well as the movement and relaxation time of
the body, is of minor influence on the release of the
biologically active ingredient.

The weight ratio of cushioning beads to
biologically active ingredient-loaded beads is not
critical to the present invention, and depends upon
the acceptable amount of dose dumping which can be

- 73 -

tolerated.   Increasing   the   percentage   of   the
cushioning beads decreases the amount of dose dumping.
Dose dumping can be attributed to the failure of the
sustained-release properties of the biologically
active ingredient, which is the result of cracks
occurring in the membrane of the beads that are
induced by the mechanical stresses of compaction.
Generally, the weight ratio of cushioning beads to
biologically active ingredient-loaded beads is about
20:80-90:10, preferably about 50:50-75:25.

When viscosity enhancer beads are present in the
tablet, the weight ratio of cushioning beads to
biologically active ingredient loaded-beads to
viscosity enhancer beads is not critical to the
present invention, and depends upon the desired
viscosity required to keep the biologically active
ingredient-loaded beads suspended until the suspension
is swallowed by the patient. Generally, the viscosity
enhancer, either as individual beads or as a component
of the biologically active ingredient-loaded beads, is
present in an amount to achieve an apparent viscosity,
at   20°C,   of   30-3000   mPa.s,   preferably   of
500-1000 mPa.s. This viscosity is required to form a
homogenous suspension, depending on the size and
density of the biologically active ingredient-loaded
beads.

The   tablets   can   also   contain   components
traditionally employed in the formulation of tablets,
e.g., a flavoring agent, a sweetener, a colorant
agent, and a buffering agent, such as those listed
above, as well as a lubricant, e.g., magnesium
stearate, hydogenated vegetable oil, or stearic acid.
Tabletting of the beads is effected by the type
and ratio of the cushioning beads surrounding the
biologically active ingredient-loaded beads, the

physical characteristics of the biologically active ingredient-loaded beads and other components present in the system, the type and characteristic of the coating material, if any, employed with the biologically active ingredient-loaded beads, and the compression pressure used in the production of tablet compacts.

The compression pressure used in the production of tablet compacts is not critical to the present invention, and depends upon the nature and percentage of the cushioning beads, the biologically active ingredient-loaded beads, and other excipients included in the tablet, such as a viscosity enhancer or lubricant, which is added to facilitate the ejection of the tablet from the die following compression. Typical lubricants employed, e.g., magnesium stearate, tend to produce tablets with lower tensile strengths. Generally, the compression pressure will be about 5-50 MPa, preferably about 10-30 MPa.

When using a viscosity enhancer, the tablets of the present invention are useful for preparing an immediate release suspension (when no coating material is used on the biologically active ingredient-loaded beads or when no polymer is incorporated in the matrix system of the biologically active ingredient-loaded beads) or a sustained release suspension (when a coating material is used on the biologically active ingredient-loaded beads or when a polymer is incorporated in the matrix system of the biologically active ingredient-loaded beads), and rapid disintegration when the tablet is immersed in an aqueous solution. The tablets of the present invention disintegrate in a couple of seconds, which has heretofore not been achieved in the art, and give rise to a formation of a suspension *in situ* over a

- 75 -

period of less than 1.0 min, which also heretofore, has not been achieved in the art.

The *in situ* suspension is useful for preparation of sustained release liquid products for either elderly or pediatric patients who cannot swallow tablets or capsules, or for patients who require large doses of biologically active ingredients, where swallowing large dosage forms is difficult.

The following examples are provided for illustrative purposes only and are in no way intended to limit the scope of the present invention.

In the Example below, all percentages are weight percentages, unless otherwise indicated.

EXAMPLE 1
Selection and Processing of the Viscosity Enhancer
I.   Introduction

Many factors play a role in the selection of a viscosity enhancer to be incorporated in tablet systems intended to be dispersed instantaneously to form suspensions. Most important of which is the concentration needed in the dispersed phase to impart sufficient structure and/or viscosity to reduce the sedimentation or floating of the particles. Despite the fact that such tablet systems are not intended to be swallowed as such by the patient, it is desirable from a practical point of view to choose a polymer which requires the least possible concentration so that least bulky tablets can be produced. Apart from the viscosity produced by the polymers, the ideal polymer should preferably exhibit a minimum yield value (plastic flow) irrespective of the viscosity, so that sedimentation would not occur (Meyers et al, *J. Soc. Cosmet. Chem.*, $\underline{10}$:143-154 (1959)). The second factor to be considered is the rate of build-up of

- 76 -

viscosity which should be fast enough to provide adequate suspension properties, yet should not interfere with the disintegration of the tablet.

In studying the rheology of different polymers, it is essential to simulate the rate of shear which will be encountered in administering the dosage form. Since most of the polymers exhibit plastic or pseudoplastic flow properties, viscosity cannot be determined without referring to the shear rate. This is because in Non-Newtonian systems, the shear rate is not proportional to shear stress. The shear rate exerted on the suspending vehicle by the sedimentation of the suspended particles is in the range of 0.001-0.1 sec^{-1} (*Rheological Properties of Cosmetics and Toiletries*, Marcel Dekker, Inc. (1993)). For larger-size particles, such as that encountered with spheres, the shear rate is expected to be higher, especially when considering the fact that the dispersed particles exhibit an additional momentum imposed by the stirring action which occurs when the extemporaneous self-suspending tablet is stirred in water. Thus, the viscosities of the various polymers were studied over a shear rate range up to 1.0 sec^{-1} using a couette attachment.

The couette (cup and bob) attachment offers the advantage of its ability to test low viscosity fluids so that valid measurements over the entire shear range can be measured. However, when plastic flow is encountered, the cup and bob attachments are more likely to produce variable shear stress across the distance between the shearing head and the container walls, resulting in a "plug effect". This "plug effect" can be partially eliminated by using the largest diameter bob possible, or by using the

- 77 -

appropriate cone and plate attachments.   In the
current work the "plug effect" was minimized by the
use of the largest diameter bob possible.

II.   <u>Experiments</u>

    A.   <u>Materials</u>

    Eight rapidly hydrating viscosity enhancers were
evaluated for their rheological properties. Carbopol®
EX214 grade (a previously neutralized salt of
carbomer), Visquick® 21 and 11 (a combination of
2:1 and 1:1 guar gum/xanthan, respectively),
Insta*Thick Xanthan®, Insta*Thick Sodium Alginate®,
Insta*Thick Carrageenan®, Insta*Thick Pectin® and
Insta*Thick Gum Arabic®. The Insta*Thick® product line
is a specially formulated line of viscosity enhancers
produced by Zumbro Inc. to provide an
instantaneous-dispersing quick-hydrating viscosity
enhancers. These polymers, and all other materials
used in the powder-layering and extrusion
spheronization experiments are listed in Table 1
below.

TABLE 1

Material	Trade Name	Supplier	Lot#
Carbomer, N.F. (salt)	Carbopol® EX214	The B.F. Goodrich Company, Cleveland, OH	YJ002D3
Guar gum/Xanthan (2:1)	Visquick® 21	Zumbro, Inc. Hayfield, MN	G336-4
Guar gum/Xanthan (1:1)	Visquick®11	Zumbro, Inc. Hayfield, MN	G173-4
Xanthan Gum, N.F.	Insta Thick Xanthan®	Zumbro, Inc. Hayfield, MN	G143-4
Sodium Alginate, N.F.	Insta Thick Sodium Alginate®	Zumbro, Inc. Hayfield, MN	G044-4
Carrageenan, N.F.	Insta Thick Carrageenan®	Zumbro, Inc. Hayfield, MN	G073-0
Pectin, USP	Insta Thick Pectin®	Zumbro, Inc. Hayfield, MN	G097-4
Acacia, N.F.	Insta Thick Gum Arabic®	Zumbro, Inc. Hayfield, MN	G234-4
Microcrystalline Cellulose, N.F.	Avicel® PH101	FMC Corp., Philadelphia., PA	1173
Mannitol, USP	Mannitol Powder	SPI-Polyols, Inc. New Castle, DE	31631-6
Croscarmellose Sodium, N.F.	Ac-Di-Sol®	FMC Corp., Philadelphia. PA	T 314
Crospovidone, N.F.	Polyplasdone-XL®	ISP Technologies, Inc., Wayne, NJ	S50427
Povidone, USP	Plasdone® K29-32	ISP Technologies, Inc., Wayne, NJ	TX40430C
Povidone, USP	Plasdone© K90	ISP Technologies, Inc., Wayne, NJ	A40903
Sugar spheres, N.F.	Nu-Pareil® (18-20 Mesh)	Crompton Knowles Mahwah, NJ	

Solutions of different concentrations of each polymer (Table 2 below) were prepared 24 hrs in advance to ensure complete hydration. Dispersions were prepared by slowly sprinkling a known quantity of each polymer into the vortex of a rapidly stirred

premeasured quantity of distilled water using a
Nuova II Stir Plate (Model SP18425, Thermolyne Corp.,
Dubuque, IO). The dispersions were stirred for an
additional 10 mins, and saved in bottles until they
5 were evaluated.

TABLE 2

Viscosity Enhancer	Solution Concentration (% weight/volume)
Carbomer EX214	0.2%, 0.175%, 0.15% and 0.1%
Visquick® 21	1.0%, 0.75%, 0.5%, 0.25% and 0.125%
Visquick®11	1.0%, 0.75%, 0.5%, 0.25% and 0.125%
Insta Thick Xanthan®	1.0%, 0.5%, 0.35%, 0.25% and 0.15%
Insta Thick Sodium Alginate®	2.0%, 1.5%, 1.0% and 0.5%
Insta Thick Carrageenan®	2.0%, 1.5%, 1.0% and 0.5%
Insta Thick Pectin®	4.0%, 2.0%, and 1.0%
Insta Thick Gum Arabic®	8.0%

A Dynamic Stress Rheometer SR-200 (Rhiometrics,
Piscataway, NJ) with a couette (cup and bob)
attachment was used to evaluate the viscosity of the
different solutions of each polymer over a range of
5 shear rate. A couette provides a large surface area
to obtain low stress measurements for low viscosity
fluids. Viscosity measurements using controlled
stress were taken during the application of a stress
that was linearly ramped.

10   Attempts to measure the hydration rate of some of
the polymers listed in Table 1 above were made by
sprinkling a known quantity of the polymer into the

- 80 -

vortex of 20 ml of distilled water placed directly in
the cup of the couette. Stirring of the dispersion
was made via a tiny magnetic bar placed in the couette
cup which in turn was placed over a magnetic stirrer.
Stirring time was restricted to 30 sec, afterwhich the
magnetic bar was removed from the cup and the
viscosity of the dispersion in the couette was
monitored as a function of time at a fixed shear rate
of 0.1 sec^{-1}.

B.   Powder-Layering of Carbomer
      EX214 on Sugar Beads

An Aeromatic® MP-1 with rotoprocessor module
(Figure 2) (Niro-Aeromatic, Columbia, MD) was used to
layer carbomer EX214 onto 18-20 mesh size cut of sugar
spheres. Polyvinyl pyrollidone (PVP) dissolved in
ethanol (USP) was used as the binder solution. The
carbomer EX214 powder was fed through a screw feeder
into the rolling bed of the sugar spheres after a
1.0 min lag period was allowed for the binder solution
to wet the beads. Three different batches of
powder-layered beads were produced by using three
different alcoholic binder solutions: 2.0% PVP
K29-32, 2.0% PVP K90, and 5.0% PVP K90. The layered
beads were air-dried at room temperature overnight to
allow the alcohol to evaporate.   Table 3 below
summarizes the process used to produce the layered
beads.

●

- 81 -

TABLE 3

Materials:	
Carbomer EX214 powder Binder solution	2.0% or 5.0% alcoholic PVP K90 (Povidone, ISP) 2.0% alcoholic PVP K29-32 (Povidone, ISP)
Sugar spheres (18-20 mesh)	1000 g
Equipment:	
Aeromatic MP-1 with rotoprocessor module	
Processing Conditions:	
Initial charge	1000 g
Number of nozzles	1
Nozzle tip opening	1.0 mm
Atomization air pressure	1.75 bar
Gap pressure	1.0 bar
Spray rate of binder solution	8.9-9.8 g/min
Powder feed rate	3.9-4.4 g/min
Rotary disc speed	194 RPM
Total spraying time of the binder	45-55 min

The yield was calculated as the amount of
carbomer EX214 sticking to the surface of sugar
spheres relative to the amount added. The percentage
load by weight was determined from the net weight of
5   the dried product minus the initial weight of sugar
spheres relative to the net weight of the dried
product. The yield and percentage load by weight for
the three different binder solutions are listed in
Table 4 below. Magnified photographs of two selected

- 82 -

batches of carbomer EX214 layered-beads were taken at
a magnification of 23X using a Wild Leipz microscope
(Wild Leipz USA Inc., Rockleigh, NJ) connected to a
Sony Video Printer (Model UP5000, Sony Corp., Tokyo,
Japan).

TABLE 4

Binder Solution	Rate of Addition of Solution (ml/min)	Rate of Addition of Powder (g/min)	Yield	% Load by Weight
5.0% PVP K90	9.8	4.4	96.3%	15.4%
2.0% PVP K90	8.9	3.9	71.53%	12.2%
2.0% PVP K29-23	8.9	4.2	73.0%	13.9%

C.   Release of Carbomer EX214 from Layered Beads
Each formulation was tested for the release of
carbomer EX214 as a function of time by dispersing a
precalculated amount of the beads sufficient to
produce a concentration of approximately
0.175% carbomer in 2000 ml of distilled water placed
in a 4.0 liter beaker stirred at a fixed speed (level
8) via a Nuova II Stir Plate (Model SP18425,
Thermolyne Corp., Dubuque, IO). Samples of the
supernatant were withdrawn via a syringe fitted with
a stainless steel filter (200 μm opening) at 0.5, 1.0,
1.5, 3.0, 5.0, and 30 min. The amount of carbomer
EX214 released was measured by titrating the
carboxylic acid residues of carbomer EX214 in those
samples against 0.01 N NaOH to a pH end-point of 9.5.
At pH 9.5, all of the COOH groups are neutralized
since the pKa of carbomer EX214 is between 7 to 8. A
Multi-Dosimat E145 automatic titrator (Brinkmann
Instruments, Westbury, NY) was used. The percentage

of carbomer EX214 released at each time point was calculated as the ratio of the volume of the 0.01 N NaOH required to neutralize the COOH groups of the carbomer EX214 present in the supernatant at that time point relative to that released at 30 min, at which time all of the carbomer EX214 is assumed to be released, multiplied by 100. The release profiles for the three different batches using the three different binder solutions were determined in triplicate.

D.   Extrusion-Spheronization of Carbomer EX214

Different formulations containing 30% carbomer EX214 together with other excipients (Table 5 below) were prepared.

TABLE 5

Code	MCC:Mannitol	%Ethanol/ H2O	Volume (ml)	Disintegrant Level & Type
Y3	100:0	50%	1400	No Disintegrant
Y4	100:0	50%	1400	8.0% Croscarmel -lose Sodium
Y5A	100:0	50%	1600	8.0% Crospovidone
Y6A	100:0	50%	1400	16% Croscarmel -lose Sodium
Y7A*	100:0	50%	1800	16% Crospovidone
Y8A	50:50	50%	1200	No Disintegrant
Y10	50:50	50%	1300	8.0% Croscarmel -lose Sodium
Y9A	50:50	50%	1500	8.0% Crospovidone
Y11	50:50	50%	1300	16% Croscarmel- lose Sodium
Y12	50:50	50%	1700	16% Crospovidone
X4A	100:0	25%	1400	No Disintegrant

* This batch was generated in duplicate to check reproducibility.

The effect of certain formulation variables involved in the production of carbomer EX214 spheres

by extrusion-spheronization was investigated to help
in elucidating the significant factors affecting the
release of carbomer EX214. The following factors were
studied:

5   •   Effect of water-soluble excipients (as
exemplified by mannitol) on the release of carbomer
EX214 from spheres.

    •   Effect of intra-sphere disintegrant type
(croscarmellose sodium and crospovidone) and level

10   (0%, 8.0%, and 16.0%) on the release of carbomer from
spheres.

    •   Effect of the granulating vehicle composition on
the release of carbomer from spheres.

    The powder mass of each formulation (1.0 Kg) was

15 dry blended in a planetary mixer (Hobart Kitchen Aid
Model K 45 SS, Hobart Corp., Troy, OH) for 5 min.
This was followed by the addition of the granulating
solution. A 50% alcohol-water system was used as the
granulating agent. One additional formulation

20 containing 30% carbomer EX214 in MCC was produced
using 25% alcohol/water to study the effect of a lower
alcohol level on the release of carbomer EX214. The
required volume of the granulating liquid was added
slowly over a period of 1.0 min. Wet granulation was

25 continued for an additional 9.0 min until a cohesive,
plastic mass was achieved. The wet mass was extruded
through a 1.0 mm screen using the Nica® E-140 extruder
(Niro-Aeromatic, Columbia, MD). The extrudate was
spheronized at 500 RPM for 5.0 min using the Nica®

30 S-450 spheronizer (Niro-Aeromatic). Spheres produced
were tray-dried at room temperature for 48 hrs, and
the dried product was stored in double plastic bags
for later evaluation.

- 85 -

E.   Release of Carbomer EX214 from Beads
      Produced by Extrusion-Spheronization

Each formulation was tested for the release of
carbomer EX214 as a function of time by dispersing a
precalculated   amount   (11.66   g)   of   the   beads
(20-30 mesh cut) sufficient to produce a concentration
of 0.175% carbomer EX214 in 2000 ml of distilled water
placed in a 4.0 liter beaker stirred at a fixed speed
(level 8) via a Nuova II Stir Plate. Samples of the
supernatant liquid were withdrawn via a syringe fitted
with a stainless steel filter (200 μm opening) at 0.5,
1.0, 1.5, 3.0, 5.0, and 30 min.   The amount of
carbomer EX214 released was measured by titrating the
carboxylic acid residues of carbomer EX214 against
0.01 N NaOH solution to a pH end-point of 9.5, at
which point all of the COOH groups were neutralized
(the   pKa   of   carbomer   is   between   7   to   8).
A Multi-Dosimat E145 automatic titrator (Brinkmann
Instruments, Westbury, NY) was used.

The percentage of carbomer released at each time
point was calculated as the ratio of the volume of the
0.01 N NaOH required to neutralize the COOH groups of
the carbomer EX214 present in the supernatant at that
time point relative to that released at 30 min, at
which time all the carbomer EX214 is assumed to be
released, multiplied by 100. The release profile for
each formulation was determined in triplicate.

III. Results and Discussion

      A.   Selection of Polymers to be Used
            as Viscosity Enhancers

The viscosity of different concentrations of
carbomer EX214, Visquick 11, Visquick® 21, and
Insta Thick Xanthan® as a function of the shear rate
studied can be found in Figures 5-8, respectively.

- 86 -

Insta Thick Sodium Alginate®, Insta Thick Carrageenan®, Insta Thick Pectin® and Insta Thick Gum Arabic® produced very low viscosities, even when used at high concentrations. Thus, these polymers were eliminated as potential candidate to be incorporated in the extemporaneous self-disintegrating tablet system.

When examining Figures 5-8, it is quite clear that these polymers exhibit shear thinning properties (viscosity decreasing with increasing shear rate). The initial increase in the viscosity at shear rates less than 0.1 sec^{-1} can be attributed to the "plug effect".

Ellis et al (*Diabetic Medicine*, $\underline{8}$:378-381 (1991)) developed a method for monitoring the hydration rate of guar gum which involved the measuring of the change of viscosity at discrete time intervals over a period of 5 hrs using a Brookfield RVT rotoviscometer. Their initial hydration experiments encountered difficulties due to the aggregation and clump formation after the addition of water. This led to large differences in viscosity between replicates. To overcome this problem the guar samples were hydrated in screw-top glass jars which were rotated end-over-end for a minimum period of time needed to prevent aggregation.

A determination of the hydration rates of the polymers listed in Table 1 above by monitoring the change of viscosity as a function of time was attempted. Aggregation and clumping defects were observed. In some cases, the clumping was so marked that viscosity could not be measured, and in other cases, this led to large differences in the viscosity between replicates. Attempts of initially hydrating the polymers by mixing them in bottles to prevent aggregation resulted in almost complete hydration,

- 87 -

thus further increases in viscosity could not be
monitored.

Moreover, since the polymers to be used in the
tablet system were further processed so as not to
interfere with the disintegration process, measurement
of the hydration rate of the polymer in the powder
form is expected to be different from that in the
processed state (powder-layering or
extrusion-spheronization). Thus, the selection of the
best polymer candidate to be incorporated in the
tablet system was solely confined to its ability to
increase the viscosity at the lowest possible
concentration, rather than its hydration rate.

An apparent viscosity range of 30-3000 mPa.sec
was determined by Kimon (European Patent 0 273 005;
and U.S. Patent 4,886,669) to be appropriate to keep
methyl xanthines-loaded beads (0.2-1.0 mm in size)
suspended. Figure 9 represents a plot of the
viscosity produced by different polymer candidates at
different concentrations as a function of the shear
rate range believed to be exerted by the suspended
particles. It is clear that carbomer EX214 achieved
the required viscosity range at a relatively low
concentration (0.175%).

     B.   Powder-Layering of Carbomer EX214
              on Sugar Beads

Initial attempts of layering carbomer 971P using
water as the binder solution failed. The idea behind
using water as the binder solution was that it was
expected that once the carbomer 971P powder comes in
contact with the water-wetted surfaces of the beads,
part of the carbomer would hydrate and would act as
in situ binder for the remainder of the carbomer 971P
powder. However, this was not the case, and the

- 88 -

carbomer 971P grade was instead hydrating and causing agglomeration of the beads, preventing the free-rolling essential for successful powder-layering. The water, as a binder solution, was later replaced with a 5.0% aqueous solution of hydroxypropylmethyl cellulose. This did not provide any improvement as the beads continued to agglomerate.

These initial attempts suggested that there was a need to incorporate the binder in a non-aqueous solution which would not cause the carbomer 971P to hydrate rapidly. Polyvinyl pyrollidone (PVP) dissolved in ethanol was considered as a possible candidate. However, carbomer 971P has considerable solubility in ethanol, and hydration of the polymer could not be avoided, resulting in bead agglomeration. The partially-neutralized grade of carbomer (the EX214 grade) has minimal solubility in alcohol. Thus, further work was confined to layering carbomer EX214 using alcoholic PVP K29-32 or K90 as the binder solutions.

In the layering of carbomer EX214 on the surface of sugar spheres to enhance its dispersibility, two processing variables were studied. The first was the effect of similar alcoholic solutions of two different grades of PVP (K29-32 and K90) on the yield, percentage loading, and release profile as a function of time. The second was the effect of different concentrations of the PVP K90 binder solutions on the yield, percentage loading, and release profile of carbomer EX214 as a function of time.

Spray rate and powder application rate are considered to be the most critical variables in the powder layering process. Adding the powder too slowly leads to a wet bed and agglomeration of pellets. Adding the powder too quickly results in a dry bed

- 89 -

with excessive loss of powder through the exhaust
system and powder caking on the walls of the pan.
Equally important is that the surface of the pellets
will vary depending on the conditions of the bed.
Pellets layered in a "dry" bed often have a rough
surface. Pellets layered in a "wet" bed will have
smoother surfaces, but the batch will have an
increased number of twins and triplets. The slight
roughness on the surfaces of the final product seen in
magnified photographs can be attributed to the poor
flowability observed when the carbomer EX214 was
flowing through the screw feeder, rather than
sub-optimal balance between spray rate and powder feed
rate. This poor flowability introduced some powder
lumps into the rolling bed thus causing a degree of
surface roughness in the end product. Similar
concentrations of PVP K29-32 and K90 produced a
similar degree in surface roughness.

    C.   Effect of Binder Concentration and Type
          on the Yield and Percentage Loading

        In order to study the effect of the binder
concentration and type on the yield and percentage
loading, the spray rate and powder application rate
were fixed to approximately 9.0 ml/min and 4.0 g/min,
respectively.   The two binders studied at the
2.0% level showed similar yields and percentage
loadings as seen in Table 4 above, indicating that the
binder types studied had no effect on the yield and
percentage loading. The 5.0% K90 formulation produced
higher yield and higher percentage loading than the
2.0% K90 formulation, which can be attributed to the
stronger adhesive power of the more viscous solution
of 5.0% K90 when compared to that at the 2.0% level.

- 90 -

Thus, more carbomer EX214 was sticking to the sugar spheres.

    D.   Effect of Binder Type on the Release of Carbomer EX214 from Powder-Layered Beads

When the carbomer EX214 layered beads were dispersed in water, the outermost layer of the polymer became hydrated, thereby impeding further penetration of water into deeper layers. The different release profiles were obtained based on the addition of a precalculated amount of the beads (calculated from the percentage load by weight - Table 4 above) sufficient to produce a final concentration of approximately 0.175% carbomer EX214 in water. Thus, beads with higher percentage loading (5.0% K90) required lower amount to achieve the desired concentration. The lower the amount of layered beads with higher percentage loading provided lower surface area available for the release of carbomer EX214, and thus resulting in slower release. This can be seen clearly with the 5.0% K90 batch which exhibits a high yield and a high percentage loading (Table 4 above), thereby giving a statistically significantly ($p < 0.05$) slower release of Carbopol EX214 in the early time points, as can be seen in Table 6 below and Figure 10.

In order to check the effect of different binders studied (K29-32 and K90) on the release profiles of carbomer EX214 from the different layered beads, batches having similar loading were compared. The 2.0% K90 and 2.0% K29-32 formulations with corresponding loading of 12.2% and 13.9%, respectively, produced similar release profiles as depicted in Table 6 below and Figure 10, indicating a negligible effect of the binder type on the release of carbomer EX214.

- 91 -

TABLE 6

Time (min)	2.0% K29-32	2.0% K90	5.0% K90
0.5*	35.63 (3.35)+	48.19 (12.05)	31.25 (5.92)
1.0**	61.16 (8.20)	63.08 (4.75)	47.62 (2.84)
1.5	79.22 (3.89)	78.01 (6.30)	89.90 (4.56)
3.0	88.63 (8.18)	88.51 (8.88)	89.90 (4.56)
5.0	91.27 (5.08)	94.73 (7.40)	96.34 (7.82)

* Significant difference exists among the formulations $p<0.1$, no difference between 2.0% K29 and 2.0% K90

** Significant difference exists among the formulations $p<0.05$, no difference between 2.0% K29 and 2.0% K90

+ Relative standard deviation

Layering of carbomer EX214 on sugar spheres or on beads containing a biologically active ingredient exposes the polymer at the surface, rather than internally in a matrix system commonly encountered in beads produced by extrusion-spheronization. Thus, it would be expected that faster viscosity build-up is associated with powder-layered beads. The presence of polymer at the surface of the beads might result in quick hydration, which might impede the tablet disintegration. Moreover, layering carbomer EX214 on the surface of beads containing biologically active ingredient makes it more system-specific, and less

- 92 -

robust to be used in other systems. Whereas, carbomer EX214 beads produced by extrusion-spheronization can be mixed with any beads containing biologically active ingredient, and compressed into a tablet, making them more diverse in application.

E.   Extrusion-Spheronization of Carbomer EX214

A major problem encountered with processing any grade of carbomer is that it becomes very tacky when wetted, which introduces handling problems, such as those encountered with wet granulation techniques prior to extrusion-spheronization. Previous workers (Chow et al, "Fabrication and Characterization of Extruded and Spheronized Beads Containing Carbopol EX214) tried to circumvent this problem by modifying the pH or the ionic strength of the granulation fluid. However, high alkalinity (B.F. Goodrich literature, Cleveland, OH) can collapse the resin structure, resulting in a permanent loss in viscosity. Moreover, soluble salts decrease the efficacy of the carbomer resin mucilages, in terms of building-up viscosity, with the di- and tri-valent cations producing more drastic loss in efficacy than monovalent cations (Charman et al, *Drug. Dev. Ind. Pharm.*, 17(2):271-280 (1991)).

The objective behind the extrusion-spheronization of carbomer EX214 powder was to formulate carbomer in a readily dispersible form capable of instantaneously generating viscosity with minimal dispersion defects in various matrices using a hydroalcoholic granulating solution to reduce the tackiness.

The percentage of carbomer EX214 released from a 20-30 mesh sieve-cut can be found in Table 7. below

TABLE 7

	100:0 MCC/Mannitol					50:50 MCC/Mannitol				
	0%	8.0% CCS*	16.0% CCS*	8.0% CP**	16.0% CP**	0%	8.0% CCS*	16.0% CCS*	8.0% CP**	16.0% CP**
Code	Y3	Y4	Y6	Y5A	Y7A	Y8A	Y10	Y11	Y9	Y12
Time (min)										
0.5	35.4 (8.7)+	35.8 (0.9)	24.4 (6.1)	39.6 (2.0)	49.0 (1.7)	42.5 (7.4)	26.9 (0.5)	33.0 (1.3)	48.8 (1.3)	48.5 (1.3)
1.0	69.3 (2.5)	66.3 (9.9)	45.4 (2.0)	67.1 (7.2)	75.2 (1.2)	61.7 (3.4)	56.1 (6.6)	56.9 (8.8)	80.4 (2.6)	71.7 (5.8)
1.5	86.5 (4.4)	86.3 (11.9)	67.3 (3.7)	91.0 (2.9)	89.9 (1.0)	74.5 (8.1)	73.1 (3.0)	72.7 (6.1)	93.1 (5.9)	86.6 (3.3)
3.0	98.5 (3.0)	94.7 (5.9)	98.0 (0.5)	97.1 (5.0)	95.9 (0.2)	100.9 (2.1)	95.3 (5.9)	98.3 (1.8)	98.6 (3.7)	94.7 (2.3)
5.0	99.8 (0.4)	96.5 (3.8)	99.2 (2.1)	98.7 (0.8)	99.3 (1.5)	100.1 (4.3)	95.4 (3.2)	96.2 (2.6)	96.3 (2.4)	98.1 (2.9)

```
*    Croscarmellose sodium
**   Crospovidone
+    Relative standard deviation
```

The effect of croscarmellose sodium and crospovidone incorporation on the release of carbomer EX214 from beads containing 100% MCC (using 50% hydroalcoholic granulating solution) are depicted

5   in Figures 11 and 12, respectively. Figure 13 represents the effect of MCC/mannitol ratio on the release of carbomer EX214 from beads containing no disintegrants. Figure 14 represents the release profiles for the two batches of Y7A prepared to check

10   for reproducibility. Figure 15 depicts the release of carbomer EX214 from different sieve-cuts of spheres; namely: 20-30 mesh and 35-40 mesh cuts, for

formulations Y3 and Y7A. Moreover, the percentage released as a function of time for formulation Y3 and X4A, whose granulating fluid alcohol/water ratio was varied from 50/50 to 25/75, respectively, is shown in Figure 16.

ANOVA analysis for the 20-30 mesh cut of the formulations prepared using a 50% hydroalcoholic solution as the granulating fluid at 0.5, 1.0, 1.5, and 3.0 min intervals revealed that a significant difference in percentage released existed only at 0.5, 1.0, and 1.5 min (p-value less than 0.00001). Regression analysis revealed that crospovidone had no significant effect on carbomer EX214 release (Figure 12), whereas croscarmellose sodium significantly decreased the release until the 3.0 min interval (Figure 11). Mannitol significantly decreased the release only at 1 min.

It seems that the carbomer-containing beads produced by extrusion-spheronization do not disintegrate but, rather, dissolve/erode as a function of time. This conclusion is supported by the fact that different sieve cuts for each of the two formulations tested revealed a significant difference in the release profile with the smaller sieve-cut (35-40 mesh fraction) releasing faster than the 20-30 mesh (Figure 15). The inability of the superdisintegrant incorporated to enhance the release of carbomer by breaking apart the beads supports the fact that disintegration is not contributing significantly to the release of carbomer EX214. This inability can be attributed to the fact that when the beads are hydrated, carbomer EX214 forms a very viscous environment, thereby preventing the disintegrants from exerting their action. The effect of croscarmellose sodium in decreasing the release of

carbomer can be attributed to the additional viscosity and gelling action imparted by the wetted croscarmellose sodium, especially when present at high levels. This is seen in Figure 11 where at the 8.0% croscarmellose sodium level, release was not affected, whereas at the 16% level, croscarmellose sodium significantly decreased the release. Crospovidone tends to be less viscous than croscarmellose sodium, therefore the release was not decreased when crospovidone was present (Figure 12). Mannitol significantly decreased the release of carbomer EX214 at 1.5 min (Figure 13). The difference among the various formulations was insignificant at 3.0 min, as detected by ANOVA testing. This is so because at that time, the majority of carbomer EX214 has been released.

The insignificant differences in the release profiles of the two batches of the Y7A (Figure 14) supports the reproducibility of the process of producing carbomer beads by extrusion-spheronization.

As the ratio of water in the granulating vehicle increases (Figure 16), the release of carbomer EX214 decreases significantly ($p < 0.05$). This can be due to the fact that as the ratio of water increases, more bonding occurs between the MCC molecules within the spheres, thereby stronger beads are produced which would dissolve slower, resulting in a slower release of carbomer EX214. This is in accordance to previous researchers findings (Millili et al, *Drug Dev. Ind. Pharm.*, 18(5):501-517 (1992)) that water granulated MCC pellets are stronger and harder than those produced using hydroalcoholic solution.

- 96 -

F.   Selection of the Processed Carbomer
      EX214 Formulation to be Incorporated
      in the Tablet System

The choice between the carbomer EX214 beads
produced   by   powder-layering   or   by
extrusion-spheronization was based on the release
property as a function of time. A faster release rate
is desired in order to ensure a quicker build-up of
viscosity. Figure 17 depicts the release profile of
carbomer   EX214   from   beads   produced   by
extrusion-spheronization (formulation Y3 containing
30% carbomer EX214 in MCC (Table 7 above)), and that
produced by powder-layering using the 2.0% K29-32 as
the binder solution (Table 6 above). The beads
produced by extrusion-spheronization released carbomer
EX214 at a faster rate than the powder-layered beads.
In powder-layered beads, the hydration of the outer
layer of carbomer EX214 impeded the penetration of
water to deeper layers, whereas in beads produced by
extrusion-spheronization, the presence of MCC seemed
to enhance the uptake of water into the inner core of
the beads, thereby producing faster hydration and
faster release of the carbomer.

Apart from the slower release rate encountered
with the powder-layered beads, powder-layering of
carbomer EX214 is a more difficult process than
extrusion-spheronization. This is so because
powder-layering requires a great deal of operator
experience. Moreover, the powder to be layered must
exhibit good flowability. Carbomer EX214 has a poor
flowability due to its fluffy and hygroscopic nature.
Atmospheric moisture is quickly absorbed by carbomer
EX214, making it more cohesive, and thereby impairing
flow.

IV.   Conclusions

Among the various polymers evaluated for their rheological properties, carbomer EX214 proved to be an ideal candidate in terms of speed of hydration, presence of yield value and lowest concentration needed to achieve an optimal viscosity required to minimize the sedimentation rate of suspended particles.

Layering of carbomer was achieved by using the EX214 grade, which does not hydrate in alcohol, together with an alcoholic PVP solution. Similar concentrations of the different grades of alcoholic PVP solutions (K29-32 and K90) produced beads with almost equivalent yield, percentage loading, and similar release profiles of carbomer EX214. Increasing the concentration of PVP in the alcoholic binder solution increased the yield, the percentage loading, but decreased the amount of carbomer EX214 released at the early time points.

Extrusion-spheronization of carbomer EX214 was achieved by using a hydroalcoholic granulating liquid to reduce the tackiness. This approach avoided the detrimental effects of ionic salts or pH modifiers on the ability of the polymer to build-up viscosity when hydrated. Increasing the water/alcohol ratio in the granulating solution decreased the amount of carbomer EX214 released as a function of time at the early time points. The size of the carbomer EX214 beads is of significant importance in determining the release profile of carbomer EX214, indicating that dissolution-erosion type of release is involved, rather than disintegration. Superdisintegrants were not able to increase the rate of carbomer EX214 released as a function of time.

- 98 -

Processing carbomer EX214 by extrusion-spheronization produced beads with faster release profiles and more carbomer EX214 loading than powder-layering. The beads containing 30% carbomer EX214 in MCC produced by extrusion-spheronization will thus be chosen as the swellable material to be included in the water-dispersible tablets to retard the sedimentation process. These carbomer beads will be mixed with biologically active ingredient-loaded beads which have been coated by a rate controlling membrane to sustain the biologically active ingredient delivery, and a filler system (cushioning beads) capable of preventing the cracking of the membrane controlling the biologically active ingredient release, and will be compressed to form a tablet. This system should disintegrate rapidly in water, thus forming a homogenous suspension which can be swallowed.

EXAMPLE 2
Production of Inert Cushioning Beads

I.   Introduction

Beads and coated beads have often been filled into hard gelatin capsules to be used either as conventional or controlled release dosage forms. The concept of tabletting coated biologically active ingredient particles is of interest, especially in the USA, since hard gelatin capsules of Tylenol were manipulated with criminal intent. However, compaction of beads poses difficult problems. If the beads have been coated by a rate controlling membrane to sustain biologically active ingredient delivery, cracking of the membrane will cause the delivery system to change the rate of biologically active ingredient delivery or

immediately release the dose. Preventing cracking is therefore of the utmost importance.

Conventional highly compactible fillers such as MCC could be mixed with biologically active ingredient-loaded beads and compressed to form tablets. However, due to particle size differences, segregation would be encountered, resulting in weight variation and content uniformity problems. Granules produced by dry or wet granulation techniques having similar size as the biologically active ingredient-loaded beads have been able to minimize the segregation due to size differences. However, the dry or wet granulation of MCC-containing mixtures decreases its compactibility (Millili et al, *supra*; and Aulton et al, *supra*).

MCC is an essential component in the production of beads by extrusion-spheronization. Though MCC is a highly compactible material, studies indicated that beads made from MCC, alone or in combination with brittle materials, such as dicalcium phosphate or lactose, are very hard and not easily deformed or broken (Millili et al, *supra*; and Aulton et al, *supra*).

Two approaches can be utilized to produce compacts containing biologically active ingredient-loaded beads coated with a polymeric membrane to sustain the biologically active ingredient action. The first approach involves the production of plastically deforming biologically active ingredient-loaded beads coated with flexible plastically-deforming polymeric membrane which will deform under pressure to form tablets while maintaining the integrity of the coating. Waxes can be incorporated in the biologically active

ingredient-loaded beads to impart a plastic component
to the deformation process. However, most
biologically active ingredient-loaded beads commonly
filled in hard gelatin capsules are hard and brittle,
and would be expected to crack under the high
compression pressures necessary for tablet production.
The second approach involves the mixing and compaction
of the biologically active ingredient-loaded beads
with softer inert cushioning beads which deform at
lower pressures during tabletting to prevent the
fracture of the membrane-coated biologically active
ingredient-loaded beads. The production of softer
inert cushioning beads containing MCC was not
successful when water was used as the granulating
agent. Replacement of part or all of the granulating
solution with alcohol to produce softer beads which
fragment at lower pressure during tabletting improved
the compactibility of those beads to some extent
(Millili et al, *supra*; and Aulton et al, *supra*), but
was not adequate to prevent the fracture of
biologically active ingredient-loaded membrane-coated
beads (Aulton et al, *supra*).

Ideal placebo "cushioning" beads intended to be
used as diluent to be mixed with biologically active
ingredient-loaded beads to prevent segregation,
whether due to size or density, should possess the
following properties:

(1) Fragment initially into progeny primary
powder particles followed by plastic
deformation. This is so because during
the compaction of the cushioning beads
with the biologically active
ingredient-loaded membrane-coated
millispheres, it is important not only

to fill the voids between the
biologically active ingredient-loaded
millispheres, but also to surround them
so that the tablet is held together by
excipient-excipient contact;

(2)   Minimize segregation propensity by
means of similar size and density;

(3)   Deform much more readily than the
biologically active ingredient-loaded
beads;

(4)   Produce rapidly disintegrating tablets
for releasing biologically active
ingredient-loaded beads; and

(5)   Have no effect on the biologically
active ingredient release kinetics.

A significant difference in the physical and
mechanical properties of beads produced by
extrusion-spheronization is observed as a result of
the drying technique used. Freeze-drying (Kleinebudde
(1994a), supra) and microwave drying (Bataille et al,
supra) of beads containing MCC, alone or in
combination with lactose, suppress the shrinking and
densification process, resulting in pellets with
higher porosities than those dried using oven or
fluid-bed drying techniques.

Disintegrants, such as starch,
superdisintegrants, such as croscarmellose sodium,
crospovidone, and sodium starch glycolate, and
hydrophilic materials, such as hydroxypropyl cellulose
can be incorporated to increase the water content of
the extruded-spheronized beads. Superdisintegrants
can be incorporated at much lower levels than regular
disintegrants to increase the water content.
Materials included in the granulating mixture to

- 102 -

increase the water level should be efficient at low
concentrations, and should not cause the extrudate to
be sticky (which results in balling during
spheronization).

5   The following describes the use of freeze-drying
to produce cushioning beads prepared by
extrusion-spheronization. The effect of different
formulation variables (type and level of
disintegrating agents and MCC/lactose ratio) on the
10   water requirement, moisture content of the fresh
undried beads, porosity, compactibility,
compressibility, and disintegration of tablets
produced from freeze-dried beads is investigated.

II.   Experiments

15   The materials used in the production of
cushioning beads, including MCC N.F. (Avicel PH101),
and anhydrous lactose N.F. (Sheffield D.T.), together
with three different superdisintegrants, are depicted
in Table 8 below.

TABLE 8

Material	Trade Name/Grade	Supplier	Lot #
MCC N.F.	Avicel® PH101	FMC Corp., Phil., PA	1135
Anhydrous lactose N.F.	Sheffield D.T.	Quest Inter'l, Norwich, NY	MRP 534301
Croscarmellose sodium N.F.	Ac-Di-Sol®	FMC Corp., Phil., PA	T320
Crospovidone N.F.	Polyplasdone®-XL	ISP Tech., Inc. Wayne, NJ	S50427
Sodium starch glycolate N.F.	Explotab® CLV	Mendell, Patterson, NY	E50774

A.   Experimental Design

A full-factorial design investigating the effect of croscarmellose concentration at three levels (0%, 4.0% and 8.0%) and the MCC/ lactose ratio at three levels (100/0, 62.5/37.5 and 25/75) with a triplicate run of the center point was implemented. Moreover, two additional formulations containing 4.0% and 8.0% of the crospovidone and sodium starch glycolate in MCC were prepared as shown in Table 9 below.

TABLE 9

	% Croscarmellose Sodium		
MCC/lactose	0%	4.0%	8.0%
100/0	✓	✓	✓
62.5/37.5	✓	✓✓✓	✓
25/75	✓	✓	✓
	% Polyplasdone		
MCC/lactose	0%	4.0%	8.0%
100%	✓	✓	✓
	% Sodium starch glycolate		
MCC/lactose	0%	4.0%	8.0%
100/0	✓	✓	✓

✓ = Number of batches made

B.   Determination of the Optimal Granulating Fluid by Image Analysis

Particle size measurement of the fresh undried beads was performed using an optical microscope (Leitz Wetzlar, Germany) fitted with a camera (MTI 65, Dage-MTI Inc., Michigan City, IN) which was cabled

directly into a microcomputer (Apple IIe, Apple computer, Cupertino, CA). The microscopic field was displayed on the computer monitor, and particle size measurements were made using a microcomputer image analysis system (Bioquant II Microcomputer System, R&M Biometrics, Nashville, TN) with a digital pad and an electronic mouse (Hipad Digitizer, Houston Instruments, Austin, TX) to demarcate the microscopic image on the monitor. A micrometer with 10 μm graduations was placed on the microscope stage, and a dimensional calibration was performed. The fresh beads were placed onto a 25 X 50 mm glass slide as soon as they were discharged from the spheronizer, and the perimeter and area of 100 different spheres were determined. From the perimeter and area, the roundness (4ΠArea/Perimeter^2) was calculated, together with the diameter calculated from the area of the projected beads.

C. Extrusion-Spheronization

In a preliminary work, each formulation listed in Table 9 above was granulated using a series of water levels. The roundness and average diameter were calculated. The optimum level was identified as that level which produced nearly round particles whose average size is similar to the aperture of the extrusion screen.

The different formulations were prepared by dry blending the powder mass of each formulation (500 g) in an Erweka® planetary mixer (Model PRS, Erweka Instruments Inc., Milford, CT) for 5 min. This was followed by the addition of the optimal amount of the granulating liquid, as determined by image analysis, over a short period of 20 sec. Wet mixing was continued for an additional 10 min with occasional

interruptions to scrape the sides of the mixing bowl.
Extrusion was carried out using a LUWA® single-screw
extruder through a 1.0 mm screen (Model EXKS-1, LCI
Corporation, Charlotte, NC) at a speed equivalent to
48 RPM.   The extrudate was immediately spheronized
using a G.B. Caleva® spheronizer (G.B. Caleva Ltd.,
Ascot, England) for 5 min at a dial reading of 12.

The initial moisture content (IMC) of the beads
was determined immediately after spheronization by
means of a Computrac® system (Model Max 50, CT
Instruments, Inc., Tempe, AZ), which measures the
moisture content by heating a known weight of a sample
until no further change in weight is produced. The
upper limit of the heating temperature was set at
105°C.   Spheres produced were freeze-dried.   The
moisture content of the freeze-dried beads was
determined after the drying cycle was complete (final
moisture content), and the dried product was stored in
double plastic bags for later evaluation.   Two
additional batches containing MCC and
8.0% croscarmellose sodium in MCC were tray-dried.

D.   Drying of the Beads Produced by
      Extrusion-Spheronization

Beads were freeze-dried using a Dura-Top® FTS
system (FTS Systems, Inc. Stone Ridge, NY).   The
freeze-drying conditions are listed in Table 10 below.
Two additional batches (the first containing MCC with
no disintegrant, and the second containing
8.0% croscarmellose sodium in MCC) were tray-dried in
a drying oven (Golton Drying Oven, Arthur Golton Co.,
Detroit, MI) at 60°C for 20 hrs in order to serve as
controls in the compaction and compression
experiments.

- 106 -

Table 10

Freezing stage		Freezing at -20°C for 2 hrs
Primary Drying	Stage I	Temperature = -20°C Vacuum = 10 mT Time = 700 min
Secondary Drying	Stage II	Temperature = 0°C Vacuum = 10 mT Time = 600 min
	Stage III	Temperature = 25°C Vacuum = 10 mT Time = 500 min
	Stage IV	Temperature = 25°C Vacuum = Atm. Pres. Until the end of run

E.   Porosity Determination of the
      Freeze-dried Beads

The porosity (ϵ) of the dried beads (18-20 mesh cut) was calculated using the following equation:

$$\epsilon = 100(1- \frac{P_a}{P_t})$$

where (P_t) is the true density and (P_a) is the granular density.

1.   True Density Measurement

True densities (P_t) of the dried beads were determined by helium displacement using a helium densitometer (Multivolume Pycnometer 1305, Micromeretics Instrument Corp., Norcross, Pittsgurgh, GA). The true volume of the sample (an average of five runs) was calculated by determining the volume of helium displaced by the sample during the test. The true density was then calculated by dividing the weight of the sample by the average true volume. For

- 107 -

some formulations, true density was measured in duplicate or triplicate to check reproducibility.

2. Granular Density

Determination of the granular density (P_a) of the
5   dried beads was made using a mercury intrusion
porosimeter at a low pressure of 20 psi (Pore Sizer
Model 9305, Micromeretics Instrument Corp., Norcross,
Pittsgurgh, GA). A 3.0 cm^3 solid sample penetrometer
having an internal stem diameter of 0.384 cm^3 was used.
10   A high pressure vacuum pump (model A20, Marvac
Scientific Manufacturing Co., Concord, CA) was used to
evacuate the system to a pressure less than 50 μm
prior to testing. Once that pressure was reached,
mercury was allowed to fill the empty space of the
15   penetrometer that was not occupied by the sample. The
penetrometer was weighed after loading the sample
prior to beginning the experiment, and after the
mercury was allowed to penetrate the sample. The
difference in weight was attributed to the weight of
20   the mercury. The volume occupied by the mercury was
calculated by dividing the gain in weight by the
density of mercury at the temperature at which the
experiment was run. The difference between the volume
of the empty penetrometer and that of mercury is the
25   granular volume of the beads. The granular density
was calculated by dividing the weight of the beads
added to the penetrometer by its measured granular
volume. For some formulations, granular density was
measured in duplicate or triplicate to check
30   reproducibility.

F. Compaction of Inert Cushioning Beads

The freeze-dried beads and the two tray-dried
batches were compressed on a single station of an

- 108 -

instrumented (Speciality Measurement Inc., Pittstown, NJ) Manesty D3B tablet press (Thomson Engineering Inc., Hoffman Estates, IL) instrumented for the upper compression pressure. The tablet press was run at 25 RPM with one functional die (1/2" flat-faced beveled edged) at different compression pressures to produce tablets with target weights of 430 mg. The angular separation between filling and compression was 180°. Compression pressures used to produce the tablets ranged from 10-40 MPa. Approximately twenty tablets were collected at 10, 15, 20, 25, 30, 35, and 40 MPa. After 24 hrs of storage, the thickness of 5 individual tablets at each compression pressure was determined using a digital micrometer (Digimatic Caliper, Mitutoyo Ltd., Andover, England). The crushing strength (P) of the tablets was determined by diametral loading in a standard motorized tester (Key Tablet Hardness Tester, Model NT-300 Key International Inc., Englishtown, NJ). The value used for P was the mean of five crushing strength determinations of tablets at each compression pressure. Tablet tensile strength (σ) in Kg/cm^2 was calculated using Equation (1) set forth above.

G. Disintegration Testing

The disintegration times for three tablets produced at compression pressures of 15 and 20 MPa were evaluated for each formulation according to a modified USP disintegration test in which distilled water at room temperature was used as the medium.

H. Studies to Monitor Changes in Bed Density

Compression studies to monitor changes in bed density were carried out using the compaction simulator located at Smith Kline Beecham (King of

flat-faced punches. The compaction simulator system consisted of an upgraded Mand (Mand Nicolet Digital Oscilloscope (Model 440)) and an IBM PS/2 containing an Excel® based software). A sawtooth displacement profile was used to control the upper punch while the lower punch, was kept stationary. Tablet weight for each material (18-20 mesh cut), determined based on the true density of the beads as determined previously via the helium pycnometer, was adjusted to obtain a tablet thickness of 3.0 mm at zero porosity. Three tablets were produced for each formulation at a compression speed of 100 mm/s. From the upper and lower punch pressure and displacement values, it was possible to calculate the thickness of the compact during a single compression event as a function of the punch pressure. From the compact weight and true density data, the relative density of the tablet during compression was calculated.

The Athy-Heckel equation (see Equation (2) set forth above) was used to analyze the relationship between relative density during compression and the applied pressure. Regression analyses were carried out on the Athy-Heckel plots over the range of 50-200 MPa. These results were then used for the determination of the yield pressure for the (18-20 mesh cut) of the different freeze-dried formulations. The hardness of the compacts was determined using a Vanderkamp VK2000 Tablet Hardness Analyzer (VanKel Industries Inc., Edison, NJ).

In order to study the mechanism of compaction of the freeze-dried beads two approaches were undertaken:

(1) For selected batches, the yield pressure values were determined at two different punch speeds to estimate the strain-rate sensitivity index (SRS)

- 110 -

strain-rate sensitivity index (SRS) according to Equation (3) set forth above. The two punch speeds tested were 100 mm/sec and 20 mm/sec; and

(2) For selected batches, the yield pressure values were determined for different sieve cuts at an upper punch speed rate of 100 mm/s. The sieve cuts studied were: 14-18, 18-20, and 20-25 mesh cuts.

I.   Scanning Electron Microscopy

The freeze-dried beads, tray-dried beads, cross-sections of some selected freeze-dried beads, together with the tablets, as well as cross-sections of the tablets produced by compacting the freeze-dried beads were photographed under a scanning electron microscope (Model: JSM-T200, Jeol Ltd., Tokyo, Japan). The samples were placed on aluminum mounts. Double-sided Scotch® tape was previously applied to the top of the mounts. Sufficient beads to cover the surface of the mounts were added, and the mounts were tapped after turning them sideways in order to remove any excess beads. For tablet compacts, slight pressure was applied to stick the sample on top of the mounts. The samples were stored overnight at 0% relative humidity in a tightly sealed plastic container, and then sputter coated (Hummer VI Sputtering System, Technics East Inc., Annandale, VA) with a gold-palladium mixture. Settings used on the sputtering system were as follows: vacuum: 75 milliTorr, voltage: 9 Volts, sputtering time: 5.0 min. The samples were observed at a working distance of 20 mm and an excitation voltage of 25 kV. Photomicrographs of representative fields were taken

- 111 -

using a 35 mm camera (Model FT-1, Konica, Japan) and
Kodak® film (TMAX 100, Eastman Kodak Co., Rochester,
NY).

III. <u>Results and Discussion</u>

5   In this Example, cushioning beads which deform at
lower pressures during tabletting were produced by
freeze-drying to prevent the fracture of the
membrane-coated biologically active ingredient-loaded
beads, and to minimize the segregation propensity due
10   to the size differences. The effect of different
formulation variables (type and level of
disintegrating agents and MCC/lactose ratio) on the
water requirement, moisture content of the fresh
undried beads, porosity, compactibility,
15   compressibility, and disintegration of tablets
produced from freeze-dried beads were investigated.

             A.   Effect of Formulation Variables on the
                   Granulating Fluid Requirement and Initial
                   Moisture Content of the Cushioning Beads
20   <u>Produced by Extrusion-Spheronization</u>

             Changing the moisture content of the wet
granulated mass prior to extrusion-spheronization has
a major impact on the size and size distribution of
beads together with other physico-mechanical
25   properties (Hasznos et al, <i>supra</i>). Thus, in order to
investigate the effect of different formulation
variables on the properties of beads produced by
extrusion-spheronization, it is essential to identify
the optimal fluid level required by each formulation.
30   The initial moisture content (IMC) of the fresh
undried beads is a function of the amount of
granulating liquid required for each formulation. The
higher the granulating fluid level used, the higher
the IMC is expected to be. The optimal fluid level

- 112 -

requirement and the IMC of the fresh undried beads after being discharged from the spheronizer can be found in Table 11 below.

TABLE 11

Formulation	Optimal Water Level (ml/500g)	IMC %
MCC	625	55.7
4.0% Croscarmellose/MCC	725	59.5
8.0% Croscarmellose/MCC	825	62.1
MCC:lactose (62.5:37.5)	300	36.8
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #1)	410	44.8
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #2)	410	44.8
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #3)	410	44.6
8.0% Croscarmellose/MCC/lactose (62.5:37.5)	500	50
MCC:lactose (25:75)	194	26.4
4.0% Croscarmellose/MCC:lactose (25:75)	277	34.1
8.0% Croscarmellose/MCC:lactose (25:75)	360	40.2
4.0% Crospovidone/MCC	650	56.8
8.0% Crospovidone/MCC	675	57.6
4.0% Sodium starch glycolate/MCC	670	56.5
8.0% Sodium starch glycolate/MCC	750	59.7

Regression analysis revealed a significant effect of the MCC/lactose ratio, croscarmellose sodium level, and crospovidone level on the IMC. No significant difference was associated with the presence of sodium starch glycolate. An increase in the MCC/lactose ratio, croscarmellose sodium level, and crospovidone level resulted in an increase in the IMC. The coefficients of regression and their corresponding p-values can be found in Table 12 below.

- 113 -

TABLE 12

Formulation Variable	Coefficient	P-Value
Croscarmellose Sodium Experiment		
MCC/lactose Ratio	0.340	2.39E-08
% Croscarmellose Sodium	1.392	4.72E-05
Crospovidone Experiment		
% Crospovidone	0.238	0.0082
Sodium Starch Glycolate Experiment		
% Sodium starch glycolate	0.500	0.1000

The regression coefficients of the % croscarmellose sodium and the % crospovidone were 1.392 and 0.2375, respectively. Thus, an increase in the IMC due to the presence of croscarmellose sodium is approximately 6 times that of crospovidone, which can be attributed to the fact that croscarmellose sodium can take up more water than crospovidone without causing gross agglomeration and size enlargement of the beads during spheronization. When higher granulation fluid levels were used, formulations containing sodium starch glycolate agglomerated during spheronization resulting in massive balling. This is due to the much higher viscosity encountered with sodium starch glycolate when used at such levels (4.0% and 8.0%) despite the fact that a low viscosity grade was used. Although superdisintegrants tend to increase the fluid level requirement and IMC, they should ideally do this without causing massive agglomeration of the beads during spheronization.

An increase in the MCC/lactose ratio was associated with an increase in the fluid level requirement and IMC. This is in accordance with the findings of others that more granulating liquid is required as the level of MCC is increased

- 114 -

(Elber et al, *supra*; Pinto   et   al,   *supra*;   and
Bains et al, *supra*).

     B.   Effect of Drying Technique on the
           Size of Cushioning Beads Produced by
           Extrusion-Spheronization

The average area diameters (d_a) of the fresh undried beads and the freeze-dried for all of the formulations, together with the area diameters for the two batches which were tray-dried, can be found in Table 13 below.

- 115 -

TABLE 13

Formulation	d_a (mm) Undried Beads	d_a (mm) Freeze-Dried Beads	d_a (mm) Tray-Dried Beads
MCC	0.99 (0.16)*	0.93 (0.13)	0.79 (0.12)
4.0% Croscarmellose/MCC	0.85 (0.15)	0.93 (0.13)	
8.0% Croscarmellose/MCC	0.89 (0.14)	0.88 (0.14)	0.68 (0.12)
MCC:lactose (62.5:37.5)	1.03 (0.14)	1.00 (0.11)	
4.0% Croscarmel -lose/MCC:lactose (62.5:37.5) (Run #1)	0.98 (0.13)	0.97 (0.12)	
4.0% Croscarmel -lose/MCC:lactose (62.5:37.5) (Run #2)	1.04 (0.14)	0.99 (0.12)	
4.0% Croscarmel -lose/MCC:lactose (62.5:37.5) (Run #3)	0.98 (0.12)	0.97 (0.13)	
8.0% Croscarmel -lose/MCC/lactose (62.5:37.5)	0.92 (0.14)	0.92 (0.16)	
MCC:lactose (25:75)	0.99 (0.17)	1.04 (0.15)	
4.0% Croscarmel -lose/MCC:lactose (25:75)	0.98 (0.14)	1.01 (0.14)	
8.0% Croscarmel -lose/MCC:lactose (25:75)	1.01 (0.13)	1.03 (0.13)	
4.0% Crospovidone/MCC	0.99 (0.16)	0.93 (0.13)	
8.0% Crospovidone/MCC	0.99 (0.11)	0.91 (0.14)	
4.0% Sodium starch glycolate/MCC	0.99 (0.11)	0.93 (0.13)	
8.0% Sodium starch glycolate/MCC	1.00 (0.18)	0.93 (0.16)	

* Relative standard deviation

As can be seen from Table 13 above, shrinking occurring during freeze-drying is minimal when compared to that seen with tray-drying. For example,

freeze-drying reduced the average size of the fresh undried beads of the plain MCC formulation from 0.99 mm to only 0.93 mm, whereas tray-drying reduced it to 0.79 mm. The same applies to the other tray-dried batch, the 8.0% croscarmellose in MCC formulation, where the average diameter was reduced from 0.89 mm to only 0.88 mm in freeze-drying, and to 0.68 mm in tray-drying. This is in accordance to the finding of Kleinebudde (1994a), *supra*, that there is a remarkable difference in the physico-mechanical properties of pellets as a result of the drying technique, with only a minor shrinking tendency during freeze-drying. Kleinebudde suggested that removing the water in the frozen state leaves a skeleton of solid materials with resultant freeze-dried pellets having a similar size to the wet pellets, as well as high porosities. Evaporation of water in an oven or fluid-bed is accompanied by a shrinking process. The resultant pellets are smaller than the wet ones and are considerably more dense.

    C.   Effect of Different Formulation Variables
         on the Porosity of Cushioning Beads Produced
         by Extrusion-Spheronization

    The granular density, true density, and the calculated porosity for the various formulations can be found in Table 14 below.

- 117 -

TABLE 14

Formulation	Granular Density (g/ml)	True Density	Porosity
MCC (Freeze-dried)	1.02	1.59	35.62
4.0% Croscarmellose/MCC (Fried-dried)	0.70	1.61	56.35
8.0% Croscarmellose/MCC (Freeze-dried)	0.65	1.62	60.25
MCC:lactose (62.5:37.5) (Freeze-dried)	0.95	1.58	39.89
4.0% Croscarmellose/ MCC:lactose (62.5:37.5) (Freeze-dried) (Run #1)	0.80	1.59	49.87
4.0% Croscarmellose/ MCC:lactose (62.5:37.5) (Freeze-dried) (Run #2)	0.81	1.59	48.75
4.0% Croscarmellose/ MCC:lactose (62.5:37.5) (Freeze-dried) (Run #3)	0.81	1.58	48.93
8.0% Croscarmellose/ MCC/lactose (62.5:37.5) (Freeze-dried)	0.69	1.60	56.54
MCC:lactose (25:75) (Freeze-dried)	1.05	1.61	43.08
4.0% Croscarmellose/ MCC:lactose (25:75) (Freeze-dried)	0.91	1.60	43.08
8.0% Croscarmellose/ MCC:lactose (25:75) (Freeze-dried)	0.83	1.60	48.11
4.0% Crospovidone/MCC (Freeze-dried)	0.94	1.55	39.38
8.0% Crospovidone/MCC (Freeze-dried)	0.90	1.56	41.90
4.0% Sodium starch glycolate/MCC (Freeze-dried)	0.85	1.59	46.45
8.0% Sodium starch glycolate/MCC (Freeze-dried)	0.65	1.64	60.65
MCC (Tray-dried)	1.35	1.49	3.84
8.0% Croscarmellose/MCC (Tray-dried)	1.17	1.63	28.4

- 118 -

Measurement of the true densities were performed in triplicate for two formulations to check for reproducibility and variability associated with the helium pycnometer measurements. The relative standard deviation for the MCC/lactose (25:75) formulation and the 8.0% crospovidone in MCC formulation were 0.47% and 0.49%, respectively. The relative standard deviations for the plain MCC formulation, the 8.0% croscarmellose sodium in MCC formulation, and the 8.0% crospovidone in MCC formulation were 1.99%, 0.5%, and 4.59%, respectively.

Regression analysis revealed a statistical significance ($p < 0.05$) of the effect of MCC/lactose ratio, as well as the presence of different superdisintegrants on the porosities of the freeze-dried beads. Increasing the MCC/lactose ratio and the different superdisintegrant levels increased the porosity of the freeze-dried beads. For tray-dried beads, the coefficients of regression and their corresponding p-values can be found in Table 15 below.

TABLE 15

Formulation Variable	Coefficient	P-Value
Croscarmellose Sodium Experiment		
MCC/lactose Ratio	0.083	0.0291
% Croscarmellose Sodium	2.607	2.76E-06
Crospovidone Experiment		
% Crospovidone	0.785	0.0127
Sodium Starch Glycolate Experiment		
% Sodium starch glycolate	3.128	0.0060

- 119 -

The effect of drying technique on the porosities of plain MCC beads and 8.0% croscarmellose sodium in MCC is seen in Table 14 above. For the MCC beads produced by extrusion-spheronization, tray-drying reduced the porosity to 3.84%, as compared to 35.62% for the freeze-dried formulation. A similar effect is observed with the 8.0% croscarmellose sodium in MCC beads, where the porosity associated with the tray-dried beads was 28.4%, as opposed to 60.25% for the freeze-dried batch. This can be attributed to the shrinking phenomenon associated with tray-drying. Croscarmellose sodium increased the porosities of both dried beads formulation to a similar degree, regardless of the drying technique utilized.

Sodium starch glycolate and croscarmellose sodium increased the porosity to a greater extent than crospovidone, as reflected in their corresponding regression coefficients. Moreover, an increase in the porosity of the freeze-dried beads was observed with increasing the MCC/lactose ratio. The increase in porosity can be attributed to the higher water content of the freshly spheronized beads (IMC). Thus, beads with higher IMC's exhibited higher porosities. Regression analysis revealed that increasing the IMC of the freeze-dried beads by 0.478% tends to increase the porosity of the corresponding compacts by one unit (close to significance relationship, p=0.05).

        D.   Effect of Formulation Variables on the
              Compactibility of Dried Beads Produced
              by Extrusion-Spheronization

The compaction of the two tray-dried formulations containing plain MCC and 8.0% croscarmellose sodium in MCC was not possible even at a compression pressure of 40 MPa. At this high compression pressure, the

- 120 -

compacts ejected from the die, and did not have
sufficient hardness to be transferred to the hardness
tester so that their crushing strengths could not be
measured.   This was expected based on previous
researchers findings   (Millili et al, *supra*;
Aulton et al, *supra*; Çelik et al, *supra*; and
Maganti et al, *supra*) that tray or fluid-bed drying of
beads rich in MCC, were strong, hard and exhibit low
compactibility especially when water is the
granulating fluid. This can be attributed to the high
bond strength of the beads, which were hard and less
deformable, thus allowing less surface to surface
contacts for bonding to occur, thereby producing
weaker tablets. Moreover, tray-dried beads containing
MCC have a high elastic modulus so that upon the
removal of the compression force, the compressed beads
would spring back, causing a weak tablet structure
(Aulton et al, *supra*).

The effect of the incorporation of different
levels of croscarmellose sodium on the compaction of
the freeze-dried MCC beads and MCC/lactose (25:75)
beads can be found in Figures 18 and 19, respectively.
The effect of the MCC/lactose ratio at 0% and
8.0% croscarmellose sodium levels can be found in
Figures 20 and 21, respectively. Figure 22 represents
the compaction profiles of the center point
(4.0% croscarmellose sodium in MCC/lactose
(62.5:37.5)) which was run in triplicate to check for
reproducibility. Figures 23 and 24 represent the
effect of crospovidone and sodium starch glycolate
incorporation on the compaction of freeze-dried MCC
beads. The effect of incorporation of different
superdisintegrants at a 8.0% level on the compaction
profiles of freeze-dried MCC beads can be seen in

Figures 25. Figure 26 represents a summary of the different experiments performed to study the effect of different variables on the compaction of freeze-dried beads containing croscarmellose sodium at 0% and 8.0% levels. Finally, Figure 27 represents the effect of different superdisintegrants at 0% and 8.0% levels on the compaction of freeze-dried beads containing MCC.

E.   Effect of Formulation Variables on the Compactibility of Dried Beads Produced By Extrusion-Spheronization

The effect of the different variables on the tensile strength of the compacted tablets cannot be studied unless identical compression pressures are used in the generation of the different compaction profiles. Though tablets were collected at 10, 15, 20, 25, 30, 35 and 40 MPa, these compression pressures were approximate. For accuracy reasons, the compaction pressure/tensile strength data for each formulation was fitted to a straight-line model from which the tensile strengths of each compact at different compaction pressures can be predicted from the regression coefficient of each fitted line. To allow fair comparisons, the predicted tensile strengths of the different formulations at a compression pressure of 15 MPa (750 Kg) studied were calculated, and are listed in Table 16 below. Compression pressure of 15 MPa was chosen because such pressures are commonly encountered in tablet production.

Table 16

Formulation	Predicted Tensile Strength (Kg/cm^2) at a Compaction Pressure of 15 Mpa
MCC	1.97
4.0% Croscarmellose/MCC	10.56
8.0% Croscarmellose/MCC	19.17
MCC:lactose (62.5:37.5)	3.61
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #1)	10.18
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #2)	11.20
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #3)	9.91
8.0% Croscarmellose/MCC/lactose (62.5:37.5)	15.65
MCC:lactose (25:75)	8.86
4.0% Croscarmellose/MCC:lactose (25:75)	9.86
8.0% Croscarmellose/MCC:lactose (25:75)	12.37
4.0% Crospovidone/MCC	5.16
8.0% Crospovidone/MCC	5.89
4.0% Sodium starch glycolate/MCC	3.48
8.0% Sodium starch glycolate/MCC	8.29

Table 16 reveals that the strongest tablets (tensile strength of 19.17 Kg/cm^2) were produced by using the formulation composed of 8.0% croscarmellose sodium in MCC. Statistical analysis of the different variables affecting the predicted tensile strength of the tablets compressed at 15 MPa can be seen in Table 17 below.

- 123 -

Table 17

Formulation Variable	Coefficient	P-Value
Croscarmellose Sodium Experiment		
MCC/lactose Ratio	-0.089	2.343E-05
% Croscarmellose Sodium	-0.060	0.7000
Interaction (MCC:lactose x % Croscarmellose Sodium)	0.023	1.852E-06
Crospovidone Experiment		
% Crospovidone	0.4892	0.1108
Sodium Starch Glycolate Experiment		
% Sodium starch glycolate	0.7898	0.0807

The MCC/lactose ratio is of significant
importance in predicting the tablet tensile strength.
Decreasing the level of MCC produced tablets with
higher tensile strengths (Figure 20). This is seen
5   numerically in Table 16 above when comparing the plain
MCC formulation, MCC/lactose (62.5:37.5) formulation,
and the MCC/lactose (25:75) formulation with their
corresponding tensile strengths of 1.97, 3.61, and
8.86, respectively. This can be attributed to the
10   fact that increasing the level of MCC in the spheres
increases their hardness and strength by the formation
of strong adhesive hydrogen bonding (Millili et al,
supra; and Aulton et al, supra). Hard beads
containing MCC exhibit sufficient deformation to
15   produce tablets. Crospovidone (Figure 23) and sodium
starch glycolate (Figure 24) had no statistically
significant effect on the tensile strength of the
compressed tablets (sodium starch glycolate was only
significant at p-value of 0.1).

- 124 -

A statistically significant interaction between croscarmellose sodium and MCC/lactose ratio on the tensile strength of the compacts was found (Table 17). Increasing the percentage of croscarmellose sodium in the formulation predominantly containing MCC produced compacts with higher tensile strength than if such an increase occurred in a lactose-predominant formulation. This is seen in Figures 20 and 21 where in the absence croscarmellose sodium, higher MCC/lactose ratio produced tablets with lower tensile strengths (Figure 20). As the concentration of croscarmellose sodium increased to 8.0%, an increase in the MCC/lactose ratio produced tablets with higher tensile strengths (Figure 21). For beads containing water-soluble materials, such as lactose, it is not unreasonable to anticipate the presence of solute molecules of this component which have dissolved in the aqueous granulating fluid during the wet massing stage. Water removal from those beads during drying following spheronization could lead to the formation of solid bridges within the spheres by fusion at the points of contact of the primary powder particles. This will result in a greater degree of bonding, and hence the formation of relatively strong beads. However, the type of bonds formed in plain MCC beads is different from the solid bridges encountered with lactose (Dyer et al, *supra*; and Aulton et al, *supra*). Hydrogen bonding seems to produce stronger beads than those of lactose. Thus, MCC beads are stronger and less easily deformable, resulting in compacts with lower tensile strength (Figure 20). In the presence of 8.0% croscarmellose sodium in MCC, the high porosity associated with the high granulation fluid requirement decreased the hydrogen bonding between adjacent MCC molecules, resulting in softer beads

which will deform readily upon the application of
pressure to give hard tablets. In formulations
dominated by lactose, the presence of 8.0%
croscarmellose sodium increased the water requirement
5   and porosity to a lesser extent, but those beads were
still hard due to solid bridge formation.

Figure 22 demonstrates the reproducibility of the
compaction profiles observed with three different
batches of a similar formulation. Figures 25, 26 and
10   27 show the superiority of croscarmellose sodium over
both crospovidone and sodium starch glycolate in
improving the compactibility of the freeze-dried
beads.

Thus, combining both MCC and croscarmellose
15   sodium in the production of freeze-dried cushioning
beads by extrusion-spheronization produced the most
highly compactible beads, which upon compaction,
produced tablets with the strongest tensile strengths.

Moreover, regression analysis revealed that
20   increasing the porosity of the freeze-dried beads by
0.467% tends to increase the tensile strength of their
corresponding compacts by one unit (p=0.00127).

F.   Disintegration Study
The disintegration times of the tablets produced
25   by compressing the freeze-dried beads of different
formulations at compaction pressures of 15 and 20 MPa
can be found in Table 18 below. It was observed that
at higher compression pressures, longer disintegration
times were encountered. Moreover, as the MCC/lactose
30   ratio is decreased, the disintegration time is
prolonged because lactose tends to dissolve, rather
than disintegrate.

- 126 -

TABLE 18

Formulation	Disintegration time (sec) following compression at 15 Mpa	Disintegration time (sec) following compression at 20 MPa
MCC	<5	<5
4.0% Croscarmellose/MCC	<5	14
8.0% Croscarmellose/MCC	31	110
MCC:lactose (62.5:37.5)	<5	68
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #1)	367	968
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #2)	462	890
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Run #3)	331	669
8.0% Croscarmellose/MCC/lactose (62.5:37.5)	667	848
MCC:lactose (25:75)	65	164
4.0% Croscarmellose/MCC:lactose (25:75)	550	1334
8.0% Croscarmellose/MCC:lactose (25:75)	659	673
4.0% Crospovidone/MCC	<5	<5
8.0% Crospovidone/MCC	<5	<5
4.0% Sodium starch glycolate/MCC	<5	<5
8.0% Sodium starch glycolate/MCC	7	29

The effect of different formulation variables on the disintegration time cannot be statistically analyzed because in order to do so, tablets of similar tensile strengths should be compared. Unfortunately, the compaction study necessitated that compression pressure was varied, resulting in variable tensile strengths.

G.   Studies to Monitor Changes in Bed Density
An increase in bulk density of the compacts formed by compressing the cushioning beads of the different formulations was observed with an increase

in the applied pressure. The relationship between the
applied pressure and density or porosity (Athy-Heckel
equation, see Equation (2) above), measured inside of
the die, appeared to be linear over almost the entire
range of applied pressure studied for the freeze-dried
beads, with minimal initial curvilinear region
attributed to particle rearrangement. This is so
because beads, by virtue of their spherical shape and
size, tend to exhibit minimal surface contact, thereby
the particle rearrangement tends to be rapid.

Representative Athy-Heckel plots for the
freeze-dried MCC formulations and MCC/lactose (25:75)
formulations at different croscarmellose sodium levels
can be found in Figures 28 and 29, respectively.
Figures 30 and 31 represent the Athy-Heckel plots for
the tray-dried and freeze-dried formulations
containing MCC and 8.0% croscarmellose sodium in MCC,
respectively. The yield values for all of the
freeze-dried formulations, measured in triplicate over
a compression range of 40-150 MPa at an upper punch
speed rate of 100 mm/sec, and those for the two
tray-dried batches measured over a compression range
of 40-100 MPa at an upper punch speed rate of
100 mm/sec can be found in Table 19 below.

- 128 -

TABLE 19

Formulation	Yield Value (MPa)	Relative Standard Deviation
MCC (Freeze-dried)	216.8	1.20
4.0% Croscarmellose/MCC (Freeze-dried)	220.6	2.30
8.0% Croscarmellose/MCC (Freeze-dried)	222.7	2.28
MCC:lactose (62.5:37.5) (Freeze-dried)	262.1	1.17
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Freeze-dried) (Run #1)	281.8	1.20
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Freeze-dried) (Run #2)	275.2	2.36
4.0% Croscarmellose/MCC:lactose (62.5:37.5) (Freeze-dried) (Run #3)	274.4	0.22
8.0% Croscarmellose/MCC/lactose (62.5:37.5) (Freeze-dried)	273.3	1.27
MCC:lactose (25:75) (Freeze-dried)	325.6	1.63
4.0% Croscarmellose/MCC:lactose (25:75) (Freeze-dried)	310.8	0.84
8.0% Croscarmellose/MCC:lactose (25:75) (Freeze-dried)	314.7	1.08
4.0% Crospovidone/MCC (Freeze-dried)	199.0	0.70
8.0% Crospovidone/MCC (Freeze-dried)	219.0	1.22
4.0% Sodium starch glycolate/MCC (Freeze-dried)	229.5	1.45
8.0% Sodium starch glycolate/MCC (Freeze-dried)	264.2	1.38
MCC (Tray-Dried)	174.4	1.99
8.0% Croscarmellose/MCC (Tray-dried)	166.9	0.61

Results of the regression analysis to investigate the effect of formulation variables on the compressibility (yield value) of freeze-dried beads as determined by the reciprocal of the Athy-Heckel plots

can be found in Table 20 below.   The only significant
factor was the MCC/lactose ratio.   As the MCC/lactose
ratio is increased, beads with lower yield values and
better compressibility are produced (Figure 32).   In
MCC-predominant formulations, steeper slopes (thus
lower yield values) than those of the lactose
predominant formulations are observed.   This can be
explained by the fact that lactose has a higher yield
value than MCC, thus formulations which are
predominant in lactose tend to have higher yield
values.

TABLE 20

Formulation Variable	Coefficient	P-Value
Croscarmellose Sodium Experiment		
MCC/lactose Ratio	-1.2935	1.1E-08
% Croscarmellose Sodium	0.2517	0.7327
Crospovidone Experiment		
% Crospovidone	0.2750	0.929
Sodium Starch Glycolate Experiment		
% Sodium starch glycolate	5.2925	0.065

Superdisintegrants had no effect on the yield
value.   This is depicted in Figures 28 and 29 where
parallel slopes of the Athy-Heckel plots were
observed.   The differences in the y-intercept reflect
the differences in initial density or porosity of the
beads.   For example, the formulations containing
8.0% croscarmellose have lower y-intercept values than
those which are croscarmellose-free (Figures 28
and 29).   Since the y-intercept represents the natural
logarithm of the reciprocal of porosity, then lower

y-intercept values indicate higher porosities. This
is in agreement with the porosity measurements
determined for the different beads where higher
croscarmellose sodium levels produced beads with
higher porosities.

Beads produced by tray-drying exhibited
statistically significant (p<0.0001) lower yield
values than those which were freeze-dried. This can
be seen in Table 19 above where the yield value for
tray-dried MCC formulation was 174.4 MPa, as opposed
to 216.8 MPa for the freeze-dried batch. Similarly,
the yield value for tray-dried 8.0% croscarmellose
sodium in MCC formulation was lower (166.9 MPa) than
that which was freeze-dried (222.7 MPa).

Despite the fact that tray-drying produced beads
with lower yield values (thus, higher compressibility)
than those produced by freeze-drying, tablets of no
appreciable hardness were produced when tray-dried
beads were compressed. This can be explained by the
fact that Athy-Heckel analysis is only a measure of
compressibility (reduction in volume), and cannot
predict the compactibility of the tablets.
Compactibility is a term that encompasses both
compressibility and bonding of particles. Bonding of
particles is the net result of constructive formation
of bonds by plastic deformation and/or brittle
fracture, and destructive components due to
post-compression elastic recovery. Thus, although
tray-dried beads were more compressible than their
freeze-dried counterparts, tray-dried beads did not
establish strong bonds post-compression resulting in
weaker tablets. This can be attributed to a high
post-compression elastic recovery, together with poor
bonding associated with the hard tray-dried beads
relative to those which were freeze-dried (Kleinebudde

(1993), *supra*; Kleinebudde (1994a), *supra*; Kleinebudde (1994b), *supra*). Moreover, yield values were determined at a compression pressure range of 40-150 MPa (linear region), which is much higher than the compression pressure used to produce the compacts. Therefore, the compressibility of tray-dried and freeze-dried beads cannot be used to account for the compactibility of the tablets of the different beads at lower compaction pressures.

1.   Determination of the Deformation
      Mechanism of Freeze-Dried Beads

Two studies were conducted to elucidate the deformation mechanism of the freeze-dried beads. In the first study, the yield values for selected formulations were evaluated at two punch speeds; a slow speed of 20 mm/sec and a fast speed of 100 mm/sec. Strain rate sensitivity index was then calculated according to Equation (3) above. In the second study, the yield values were evaluated for different sieve cuts of the same formulation, namely: 14-18, 18-20, and 20-25 mesh cuts.

The change in the compressibility (yield value) as a function of the compression speed rate can be found in Table 21 below, together with the strain rate sensitivity index for the different formulations studied.

- 132 -

TABLE 21

Formulation	Yield Pressure at an Upper Punch Speed Rate of 20 mm/sec (MPa)	Yield Pressure at an Upper Punch Speed Rate of 100 mm/sec (MPa)	Strain-Rate Sensitivity Index
MCC	174.98 (0.84)*	216.80 (1.20)	19.29
8.0% Croscarmellose/ MCC	181.15 (1.01)	222.70 (2.28)	18.66
MCC:lactose (25:75)	213.18 (6.01)	325.60 (1.63)	34.53
8.0% Croscarmellose/ MCC:lactose (25:75)	222.52 (0.94)	314.70 (1.08)	29.29
8.0% Crospovidone/ MCC	178.92 (1.66)	219.00 (1.22)	18.30
8.0% Sodium starch glycolate/MCC	117.61 (0.69)	264.00 (1.38)	55.45

* Relative standard deviation

A difference in the yield pressure values with changing punch speed indicates the existence of a plastic component to the deformation process (Roberts et al, *supra*) of the freeze-dried beads. This can be attributed either to a change from plastic to brittle behavior, or a reduction in the amount of plastic deformation due to the time-dependent nature of plastic deformation (Rees et al, *supra*). Thus, at slower punch speeds of 20 mm/sec the compacted beads exhibited more plastic flow than at 100 mm/sec, resulting in a statistically significant lower yield values ($p < 0.0001$). Moreover, the change in strain-rate sensitivity index (Table 21) indicates a plastic component to the deformation process, with the

formulation containing 8.0% sodium starch glycolate
showing the most sensitivity.

Materials that deform by brittle fracture tend to
exhibit relatively high yield pressure values,
irrespective of the punch speed rate utilized to
produce the compacts (Hersey et al, (1971) *supra*;
Hersey et al, (1981) *supra*; McKenna et al, *supra*;
Rees et al, *supra*; Sheikh-Salem et al, *supra*;
Fell et al, *supra*; York et al, (1973) *supra*;
de Boer et al, *supra*; Rue et al, *supra*; York, (1979)
supra; Chowhan et al, *supra*; Paronen et al, *supra*;
Duberg et al, *supra*; Marchall et al, *supra*; and
Hussain et al, *supra*). Thus, the relatively high
values of the yield pressures observed during the
compression of the freeze-dried beads, at both punch
speeds studied, indicate the coexistence of a brittle
fracture component.

In the second study to explore the deformation
mechanism of the freeze-dried beads, the compression
profiles (Athy-Heckel plots) were evaluated for
different sieve cuts (14-18, 18-20, and 20-25 mesh
cuts) at an upper punch speed rate of 100 mm/sec. If
the beads were to exhibit plastic deformation, type 1
behavior (Figure 3A) would be observed in which the
Athy-Heckel plots for different particle size
fractions of the beads would be parallel. If brittle
fracture is the predominant mechanism of deformation,
type 2 behavior (Figure 3B) would be seen in which the
initial structure of the material is progressively
destroyed so that above a certain pressure, coincident
linear relations would be obtained for all size
fractions. The use of different size fractions to
detect the predominant mechanism of deformation in
f r e e z e - d r i e d   b e a d s   p r o d u c e d   b y

extrusion-spheronization was not sensitive to detect
any difference in the Athy-Heckel compression
profiles, which were completely superimpossible. This
is due to the narrow size distribution of the beads,
which is an inherent advantage of the
extrusion-spheronization process. If the size
distribution, was wider, sieve-cuts that differ
significantly in size might have given different
compression profiles from which the mechanism of
deformation could have been elucidated.

H.   Scanning Electron Microscopy

Scanning electron micrographs (SEM's) were taken
of freeze-dried beads containing plain MCC (50X), a
cross-section of a freeze-dried bead containing plain
MCC(100X), 8.0% croscarmellose sodium in MCC beads
(50X), a cross-section of a 8.0% croscarmellose sodium
in MCC bead (100X), a cross-section of a MCC:lactose
(25:75) bead (100X), and a cross-section of a
8.0% croscarmellose sodium in MCC:lactose (25:75) bead
(100X). An SEM of tray-dried beads containing plain
MCC (50X) was also taken.

SEM's were also taken of the surface of tablet
compacts at a compression pressure of 20 MPa
containing freeze-dried plain MCC beads and
8.0% croscarmellose sodium in MCC (35X).

Comparing the SEM's depicting the freeze-dried
beads containing plain MCC and 8.0% croscarmellose
sodium in MCC reveals that the surface of the latter
is more porous. Cross-sections of these two bead
formulations clearly show that the freeze-dried beads
containing 8.0% croscarmellose sodium in MCC are more
porous than those containing plain MCC, which is due
to the higher granulation fluid requirement associated
with the presence of croscarmellose sodium. A similar

- 135 -

trend is observed in the cross-sections of the beads
containing MCC:lactose (25:75) and 8.0% croscarmellose
sodium in MCC:lactose (25:75) for the same reason.

Tray-drying of beads containing plain MCC
resulted in beads with less surface porosity than
those which were freeze-dried. This is due to the
shrinking phenomenon associated with tray-drying.

The surface of tablets compressed at a similar
compression force containing plain MCC and
8.0% croscarmellose sodium in MCC differ
significantly. Those tablets made of
8.0% croscarmellose sodium in MCC have a smoother
surface than those containing plain MCC beads, where
the boundaries of the component beads are still
visible. This is because of the difference in
porosities of the two bead systems, which resulted in
a difference in compactibility.

IV. Conclusions

Inert cushioning beads of different
compressibilities, compactibilities and disintegration
properties were produced by freeze-drying. The
optimal granulating fluid level for the different
formulations studied, as determined by image analysis
based on the size and roundness of the fresh undried
beads, was essential to investigate the effect of
different formulation variables on the properties of
the dried product.

The presence of high levels of MCC and different
superdisintegrants, especially croscarmellose,
generally increased the granulating fluid levels
requirement, thus producing freeze-dried beads with
higher porosities. Compactibility studies indicate
that in the absence of croscarmellose,
lactose-predominant formulations were more compactible

than those predominant in MCC. A major interaction was observed between MCC and croscarmellose. In the presence of high levels of MCC, croscarmellose-containing freeze-dried beads were the most compactible, producing the hardest tablets at the compression pressure ranges studied. These tablets disintegrated very quickly.

Compressibility studies revealed that formulations containing high levels of MCC exhibited lower yield values, and thus were more compressible than those formulations containing high levels of lactose. Superdisintegrants had no effect on the compressibility of beads, which could be attributed to the fact that compressibility measurements (yield values) were determined at compression forces which were higher than the ranges used in the compactibility studies. Thus, the effect of the initial porosities of the beads was diminished.

The yield values were helpful in determining the compaction mechanism of the freeze-dried beads. Freeze-dried beads exhibited both plastic deformation and brittle fracture. The presence of plastic deformation was detected by the presence of strain-rate sensitivity to the compaction process when the upper punch speed rate was varied. Brittle fracture component was detected in the relatively high yield values associated with the freeze-dried beads. The existence of both plastic deformation and brittle fracture is desired in an ideal cushioning bead system. This is so because as the cushioning beads, mixed with biologically active ingredient-loaded beads, are compacted, initial fragmentation into progeny primary powder particles would not only fill the voids between the biologically active ingredient-loaded beads, but surround them. Plastic

deformation of the fine particles would then enhance the excipient-excipient interaction producing stronger compacts.

Yield value measurements for different bead-fractions were not able to explain the mechanism of deformation due to the narrow size-range of the beads produced by extrusion-spheronization process.

Tray-drying of selected batches produced beads with smaller average diameters than those which were freeze-dried. This is due to the shrinking associated with the tray-drying process, which reduced the porosity, thereby producing hard and dense beads. The tray-dried beads were not able to form tablets of any appreciable hardness when compacted.

The success of the placebo cushioning beads produced by freeze-drying must be practically evaluated by mixing and compacting them with biologically active ingredient-loaded membrane-coated sustained release beads. The cushioning beads should minimize the segregation propensity due to size and density differences, which will affect the content uniformity and weight variation of the tablets, and should deform more readily than the biologically active ingredient-loaded beads so that fracture of the membrane is minimized. Moreover, the cushioning beads should disintegrate rapidly to release the intact biologically active ingredient-loaded beads and should not affect the release kinetics of the biologically active ingredient. This challenge will be addressed in Example 3 below.
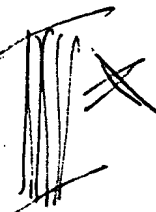
EXAMPLE 3
Formulation of Fast Disintegrating Controlled
Release Tablets from Coated Particles

I.   Introduction

Solid oral dosage forms with controlled release
properties which disintegrate after administration
into a large number of subunits, so-called multi-unit
dosage forms, show several highly important advantages
as compared to monolithic preparations. The small
particles are mixed with the contents of the stomach
and intestine and are distributed over a large area.
Thus, high local concentration of the biologically
active ingredient is avoided and the risk of
undesirable side-effects reduced. The particles
should be smaller than approximately 2.0 mm to be
transported continuously together with the food
contents through the digestive tract so that the
quality, amount and timing of food uptake, as well as
movement and relaxation time of the body is of minor
influence on the biologically active ingredient
release (Bogentoft et al, *Eur. J. Clin. Pharmacol.*,
14:351 (1987)).

Multi-unit controlled-release dosage forms have
been formulated for many years, but in most cases have
involved encapsulation in hard gelatin capsules. Such
preparations present a number of disadvantages: The
capsules themselves are relatively expensive, the bulk
density inside the capsule is low so that a larger
volume is needed for high doses, and doses cannot be
divided by splitting the capsules. On the contrary,
tablets can be produced less expensively and can be
divided without remarkable influence on the
biologically active ingredient release, which is
controlled after disintegration of the tablet by the
totality, and make up of the still intact coated

- 139 -

particles. Moreover, interest in the concept of tabletting coated biologically active ingredient particles increased significantly when hard gelatin capsules were tampered with criminal intent.

Some success with the compression of coated granules or crystals have been reported in the literature (Ventouras, *supra*; Ventouras et al, *supra*, Aulton et al, *supra*; Lehmann et al, *supra*; Juslin et al, *Pharm. Ind.*, 42:829-832 (1980); and Haubitz et al, *Drugs Made In Germany*, 38(4) (1995)). Most of these papers dealt with compacting the biologically active ingredient-loaded entities or plastically-deforming coated potassium chloride crystals with fine highly-compressible powders, such as MCC or soft highly deformable granules made up of starch. However, due to size differences, segregation would be encountered, resulting in weight variation and content uniformity problems to varying degrees.

The desirable mechanical properties of coated millispheres to be compacted into a tablet together with excipients or placebo cushioning beads should be that they are strong, not brittle and have low elastic resilience. It is important in this dosage form that the millispheres and their coatings remain undamaged and intact so that the release profile of the biologically active ingredient is not changed. Thus, the mechanical properties of both uncoated biologically active ingredient-containing millispheres and the polymeric coat responsible for sustaining the biologically active ingredient action are of crucial importance in determining the biologically active ingredient release profile when those coated beads are compressed. The presence of a film coat applied by means of an aqueous polymeric dispersion of

- 140 -

polymethacrylates or ethylcellulose also influences the mechanical properties of coated millispheres. Ethylcellulose is a very brittle material, and its films are reported to exhibit massive fracture under compression, regardless of the plasticizer or other additives used (Béchard et al, *Drug Dev. Ind. Pharm.*, 18:1927-1944 (1992)). Polymethacrylates film coatings especially Eudragit® NE 30 D, RL 30 D and RS 30D are more flexible and can withstand mechanical stresses of compression so that the release patterns are very similar or nearly the same as the uncompressed particles (Lehmann et al, *supra*; Juslin et al, *supra*; and Haubitz et al, *supra*). Despite the fact that Eudragit® NE 30 D exhibits the most flexible films, only a variation of the thickness of the coating can be used to modify the release profile. The addition of more hydrophilic or hydrophobic additives to the film are not effective, and will influence the technical behavior of the film. Eudragit® NE 30 D is commonly used with the L 30 D-55 grade for enteric coating purposes. Flexible coatings can be generated by using a mixture of Eudragit® RL and RS. By the different permeability but unlimited miscibility of both types, a wide range of permeability can be established, so that the system can be adapted to the diffusion properties of many biologically active ingredients in a narrow range of film thickness (Lehmann et al, *supra*). Increasing the polymer loading has the effect of increasing the crushing strength of millispheres, whilst simultaneously enhancing millisphere resilience (characterized by a reduction in the elastic modulus) (Aulton et al, *supra*).

- 141 -

In this Example, different biologically active ingredient-loaded beads coated with (1) ethylcellulose from organic solvent, (2) an aqueous dispersion of ethylcellulose, (3) an aqueous dispersion of polymethacrylates, and (4) a mixture of an aqueous dispersion of ethylcellulose and aqueous dispersion of polymethacrylates were evaluated. These four different biologically active ingredient-loaded membrane coated beads were blended at different percentages with the freeze-dried cushioning beads (described in Example 2 above) containing 8.0% croscarmellose sodium in MCC, and compressed into tablets at various compression forces. The release profiles of each system at different bead loads and selected compression forces were evaluated to detect changes in biologically active ingredient release profiles, and photomicrographs were taken to detect the presence of cracks associated with tablet compression.

II.   Experiments
      A.   Materials
      Four different biologically active ingredient-loaded beads coated with different polymeric membranes to sustain biologically active ingredient action were studied. All biologically active ingredient-loaded beads were produced by extrusion-spheronization utilizing MCC as the primary filler binder. The following biologically active ingredient-loaded beads were evaluated:
            1.   Propranolol hydrochloride beads
                 supplied by Wyeth-Ayerst (Rouses
                 Points, NY). These beads of 60% (w/w)
                 potency were produced by
                 extrusion-spheronization. The

sustained action was imparted by coating with ethylcellulose applied from an organic-solvent system.

2.   Phenylpropanolamine hydrochloride beads (PPA-HCl) supplied by FMC Corporation (Princeton, NJ). The uncoated beads of 38% (w/w) potency were produced by extrusion-spheronization. The sustained action was imparted by coating with 10% (w/w) ethylcellulose aqueous polymeric dispersion (Aquacoat®) plasticized with 24% (w/w) dibutyl sebacate. The coated beads were oven-dried for 2 hours at 60°C.

3.   Theophylline beads (RD010) supplied by Niro-Aeromatic (Columbia, MD). These beads, of 60% (w/w) potency, were produced by extrusion-spheronization. The sustained action was imparted by coating with 6.0% (w/w) polymethacrylic acid aqueous polymeric dispersion. The coating was composed of 48% amminomethacrylate copolymer and 9.5% methacrylic acid copolymer plasticized with 9.5% (w/w) triethyl citrate. A 2.0% (w/w) overcoat was also applied.

4.   Theophylline beads (RD011) supplied by Niro-Aeromatic (Columbia, MD). These beads of 60% (w/w) potency were produced by extrusion-spheronization. The sustained action was imparted by coating with 7.0% (w/w) mixture of polymethacrylic acid and Aquacoat® aqueous polymeric dispersions. The

- 143 -

coating was composed of 63% (w/w) Aquacoat®, 16% (w/w) methacrylic acid copolymer and was plasticized with 20% (w/w) triethyl citrate. A 2.0% (w/w) overcoat was also applied.

MCC (Avicel® PH200, FMC Corp., Philadelphia, PA) or freeze-dried cushioning beads containing 8.0% (w/w) croscarmellose sodium in MCC (Avicel® PH101), were prepared as described in Example 2 above, except that a 1.2 mm extrusion screen was used to produce larger beads. These cushioning beads were mixed and compressed with the biologically active ingredient-loaded sustained action beads.

B.   Methods

1.   Production of Tablets

Blends of various bead loads (Table 22) were prepared by mixing the biologically active ingredient-loaded membrane-coated beads (14-20 mesh cut) with either the (14-20 mesh cut) freeze-dried cushioning beads or MCC. The two filler systems were used to study the effect of filler particle size on the content uniformity and weight variation expected to be encountered due to size segregation. The batch size for each blend was 500 g and blending was performed for 10 min in a 2.0 quart twin-shell blender (Patterson Kelly Twin Shell V-Blender, Model #LB-5695, The Patterson-Kelly Co. Inc. East Stroudsburg, PA). Tablets were compressed on a single station of an instrumented rotary tablet press (Stokes RB-2, Stokes Engineering, Philadelphia, PA) utilizing a 1.58 mm flat-faced punches. The instrumentation for the measurement of compression force has been previously described by Salpekar et al, *J. Pharm. Sci.*, 63:289-293 (1974)). The angular separation between

- 144 -

filling and compression was 180°. Approximately
twenty tablets were collected at each compression
pressure (Table 22). After 24 hrs of storage, the
thickness of 5 individual tablets at each compression
force was determined using a digital micrometer
(Digimatic Caliper, Mitutoyo Ltd., Andover, England).
The crushing strength (P) of the tablets was
determined by diametral loading in a standard
motorized tester (Key Tablet Hardness Tester, Model
NT-300 Key International Inc., Englishtown, NJ). The
value used for P was the mean of five crushing
strength determinations of tablets at each compression
pressure. Tablet tensile strength (σ) in Kg/cm^2 was
calculated using Equation (1) above. Compaction
profiles consisting of the different tablets tensile
strengths for each of the tablets were generated by
plotting tensile strength versus compression pressure.

TABLE 22

Formulation	Compression Pressure (Kg/cm^2)
Propranolol Hydrochloride	
25% Propranolol Hydrochloride/ 75% Cuhioning Beads	187.2, 223.3 and 264.0
50% Propranolol Hydrochloride/ 50% Cushioning Beads	196.2, 236.9 and 277.6
25% Propranolol Hydrochloride/ 75% Avicel® PH200	155.5, 223.3 and 304.7
50% Propranolol Hydrochloride/ 50% Avicel® PH200	169.1, 209.8 and 291.1
Phenylpropanolamine Hydrochloride	
12.5% Phenylpropranolamine Hydrochloride/ 87.5% Cushioning Beads	169.1, 223.3 and 331.8
12.5% Phenylpropranolamine Hydrochloride/ 87.5% Avicel® PH200	94.5, 162.3 and 250.5
25% Phenylpropranolamine Hydrochloride/ 75% Cushioning Beads	169.1, 223.3 and 331.8
Theophylline RD010	
12.5% Theophylline RD010/ 87.5% Cushioning Beads	223.3, 331.8 and 467.5
25% Theophylline RD010/ 75% Cushioning Beads	223.3, 331.8, 467.5 and 603.1
25% Theophylline RD010/ 75% Avicel® PH200	223.3, 331.8, 467.5 and 603.1
Theophylline RD011	
12.5% Theophylline RD011/ 87.5% Cushioning Beads	223.3, 331.8, 467.5 and 603.1

- 146 -

2.   Determination of the Biologically
      Active Ingredient Content of
      Propranolol Hydrochloride Beads
      and the Content Uniformity of
      Their Compacts

The biologically active ingredient content of
beads and the content uniformity of compacted tablets
for propranolol hydrochloride were determined
according to the USP XXIII with slight modifications.
A standard curve was prepared by transferring
approximately 100 mg of the propranolol hydrochloride
(Gyma Labs, Lot #24642), accurately weighed, to a
50 ml volumetric flask. The contents were dissolved
in a solvent mixture composed of a solution of
50:50 methanol:0.012 N HCl. Five milliliters of this
solution was transferred to a 100 ml volumetric flask,
and was diluted to volume with distilled water and
mixed. Serial dilutions were made to construct the
standard curve. The biologically active ingredient
content was measured spectrophotometrically by a UV
spectrophotometer (Model UV-106A, Shimadzu Scientific
Instruments, Inc., Columbia, MD) at a wavelength of
290 nm using a quartz cuvette (1.0 cm path length).
A 98:2 water:methanol mixture was used as the blank.

The biologically active ingredient content for
the propranolol hydrochloride beads was analyzed in
triplicate. Moreover, three samples of the tablets
produced at each compression pressure of each
formulation listed in Table 22 above were randomly
selected and analyzed for propranolol hydrochloride
content. Each tablet, or a fixed weight of beads,
were weighed and transferred separately to a 100 ml
volumetric flask containing about 70 ml of a solvent
mixture composed of a solution of 50:50
methanol:0.012 N HCl. Each flask was placed in a
mechanical shaker for 24 hrs to allow the biologically

active ingredient to be released. A 24 hr period was adequate for complete release of the biologically active ingredient, as determined from the dissolution profile of uncompacted beads, where the asymptote was reached at 12 hrs. An additional solvent mixture was added to achieve a 100 ml volume, followed by shaking each flask to ensure uniform mixing. A portion of the solution was centrifuged at 1000 RPM for about 10 min to obtain a clear solution. Five milliliters of the clear supernatant was transferred to a 100 ml volumetric flask, and diluted to volume with distilled water and mixed. The content was determined spectrophotometrically at a wavelength of 290 nm using the previously constructed standard curve.

       3.   Determination of the Biologically
             Active Ingredient Content of
             Phenylpropanolamine Hydrochloride
             Beads and the Content Uniformity
             of Their Compacts

The biologically active ingredient content of beads and the content uniformity of compacted tablets for phenylpropanolamine hydrochloride was determined according to the USP XXIII with slight modifications. A standard curve was prepared by transferring about 250 mg of the phenylpropanolamine hydrochloride USP (Lot# 40560, National Pharm Manufacturing Co.), accurately weighed, to a 1000 ml volumetric flask. The content was dissolved in distilled water. Serial dilutions were made to construct the standard curve. The biologically active ingredient content was determined by HPLC-UV spectrophotometer (Waters 486 Turnable Absorbance Detector, Water Millipore Corporation, Milford, MA) at a wavelength of 254 nm. Solvent A was prepared by dissolving 1.9 g of sodium 1-hexanesulfonate in 700 ml of distilled water,

followed by the addition of 50 ml of 1.0 M monobasic
sodium phosphate and 20 ml of 0.25 N triethylammonium
phosphate (prepared by mixing 500 ml of a solution
containing 25.3 g of triethylamine and 500 ml of a
solution containing 9.6 g phosphoric acid). Solvent A
was diluted with distilled water to 1.0 liter and
mixed. The mobile phase was composed of a 100:82
mixture of solvent A and methanol after being
degassed. The chromatographic column was a
4.6 mm x 25 cm column containing C-18 packing (Type
1B-Sil 5μ C18, Phenomenex, Torrance, CA). The flow
rate was 1.5 ml per min. An accurately measured
volume of 100 μl was injected into the column, and
the peak areas were recorded and compared to those of
the standard curve in order to determine the
biologically active ingredient concentration in the
samples.

The biologically active ingredient content for
the phenylpropanolamine hydrochloride beads was
analyzed in triplicate. Three samples of the tablets
produced at each compression pressure of each
formulation listed in Table 22 above were randomly
selected and analyzed for phenylpropanolamine
hydrochloride content. Each tablet or bead sample was
weighed and transferred separately to a 100 ml
volumetric flask containing about 70 ml a distilled
water. Each flask was placed in a mechanical shaker
for 24 hrs to allow the biologically active ingredient
to be released, and was then diluted to volume with
distilled water. A 24 hr period was adequate for
complete release of the biologically active
ingredient, as determined from the dissolution profile
of uncompacted beads, where the asymptote was reached
at 12 hrs. A portion of the solution was centrifuged
at 1000 RPM for about 10 min to obtain a clear

- 149 -

solution. Five milliliters of the clear supernatant
was transferred to a 100 ml volumetric flask and
diluted to volume with distilled water and mixed. The
content was determined spectrophotometrically at a
wavelength of 254 nm using the previously constructed
standard curve.

> 4.   Determination of the Biologically
>   Active Ingredient Content of
>   Theophylline RD010 and RD011 Beads
>   and the Content Uniformity of Their
>   Compacts

A standard curve was prepared by transferring
about 125 mg of the theophylline (Lot# 12F-0630, Sigma
Chemical Co.), accurately weighed, to a 1000 ml
volumetric flask. The content was dissolved in
distilled water.   Serial dilutions were made to
construct the standard curve.   The absorbance was
measured spectrophotometrically (Model UV-106A,
Shimadzu Scientific Instruments, Inc., Columbia, MD)
at a wavelength of 271 nm using a quartz cuvette
(1.0 cm path length), and was used to calculate
concentration. Distilled water was used as the blank.

The biologically active ingredient contents for
the theophylline RD010 and RD011 beads were analyzed
in triplicate. Moreover, three samples of the tablets
produced at each compression pressure of each
formulation listed in Table 22 above were randomly
selected and analyzed for the theophylline content.
Each tablet, or a certain amount of beads were weighed
and transferred separately to a 100 ml volumetric
flask containing about 70 ml distilled water. Each
flask was placed in a mechanical shaker for 24 hrs to
allow the biologically active ingredient to be
released. A 24 hr period was adequate for complete
release of the biologically active ingredient, as

- 150 -

determined from the dissolution profile of uncompacted beads, where the asymptote was reached at 10 and 6 hrs for the RD010 and RD011 theophylline beads, respectively. An additional distilled water was added to achieve a 100 ml volume, followed by shaking each flask to ensure uniform mixing. A portion of the solution was centrifuged at 1000 RPM for about 10 min to obtain a clear solution. Five milliliters of the clear supernatant was transferred to a 100 ml volumetric flask, and was diluted to volume with distilled water and mixed. The content was determined spectrophotometrically at a wavelength of 271 nm using the previously constructed standard curve.

5.   Dissolution of Propranolol
      Hydrochloride Beads and Their
      Compacts

Dissolution studies were performed using the USP XXIII apparatus 2 (paddle method, Vanderkamp 600, Van-Kel. Industries Inc., Edison, NJ) at a paddle speed of 50 RPM. The release profiles of propranolol hydrochloride from uncompacted beads and from tablets at selected compression pressures were evaluated in triplicate to study the effect of compression on the release kinetics of the biologically active ingredient. The dissolution medium consisted of 900 ml of degassed distilled water maintained at 37°C. The dissolution apparatus was calibrated using USP prednisone and salicylic acid calibrator tablets (USP Convention Inc., Rockville, MD). Direct ultraviolet detection at 290 nm was used to assess the biologically active ingredient concentration in the dissolution medium. The dissolution medium was continuously pumped through 0.1 cm flow cells cuvettes

- 151 -

by a peristaltic pump (Rainin Instrument Co., Inc., Woburn, MA).

6. Dissolution of Phenylpropanolamine Hydrochloride Beads and Their Compacts

Dissolution studies were performed using the same apparatus and procedure described above except that manual samples of the supernatant were taken manually at 0.5, 1.0, 1.5, 2.0, 3.0, 6.0 and 24 hrs. HPLC analysis as outlined in the content uniformity of phenylpropanolamine section above was performed to determine the amount released as a function of time at a wavelength of 254 nm.

7. Dissolution of Theophylline from RD010 and RD011 Beads and Their Compacts

Dissolution studies were performed using the same apparatus and procedure followed to determine the release profile of propranolol, except that a wavelength of 271 nm was used.

8. Photomicroscopy of Tablet Compacts

Magnified photographs for fractured tablets composed of 25% propranolol hydrochloride, phenylpropanolamine hydrochloride or theophylline RD010 and 12.5% theophylline RD011 in freeze-dried cushioning beads, compacted at a compression pressure of 264.0, 331.8, 331.8 and 331.8 Kg/cm^2, respectively, were taken at a magnification of 23X to check for any fracturing of the biologically active ingredient-loaded beads occurring inside the tablet matrix as a result of the compaction process.

Moreover, surface pictures of intact tablets composed of 25% theophylline RD010 or theophylline RD011 and freeze-dried cushioning beads were taken at

- 152 -

a similar magnification to examine for any fracturing of the beads exposed to the surface. A Wild Leipz microscope (Wild Leipz USA Inc., Rockleigh, NJ) connected to a Sony Video Printer (Model UP5000, Sony Corp., Tokyo, Japan) was used.

9.   Scanning Electron Microscopy of
      Biologically Active Ingredient-Loaded
      Membrane-Coated Beads

Scanning electron micrographs for representative fields of the biologically active ingredient-loaded beads, obtained from the internal matrix of tablets composed of 25% propranolol hydrochloride, phenylpropanolamine or theophylline RD010 and 12.5% theophylline RD011 in freeze-dried cushioning beads, compacted at a compression pressure of 264.0, 331.8, 331.8 and 331.8 Kg/cm^2, respectively, were taken at a magnification of 75X, 150X and 500X using a scanning electron microscope (Model: JSM-T200, Jeol Ltd., Tokyo, Japan). After removing the excipients adhering to the biologically active ingredient loaded-beads with a brush, the beads were placed on aluminum mounts. Double-sided Scotch® tape was previously applied to the top of the mounts. Beads added to the surface of the mounts were sputter coated (Hummer VI Sputtering System, Technics East Inc., Annandale, VA) with a gold-palladium mixture. Settings used on the sputtering system were as follows: vacuum: 75 milliTorr, voltage: 9 Volts, sputtering time: 5.0 min. The samples were observed at working distance of 20 mm and an excitation voltage of 25 kV. Photomicrographs were taken using a 35 mm camera (Model FT-1, Konica, Japan) and Kodak film (TMAX 100, Eastman Kodak Co., Rochester, NY).

- 153 -

C.   Results and Discussion

The applicability of the placebo cushioning beads produced by freeze-drying (Example 2 above) was practically evaluated in this example by mixing and compacting them with different biologically active ingredient-loaded beads whose action was sustained by different polymeric membranes. The tablets contained propranolol beads coated with ethylcellulose from organic solvent, phenylpropanolamine hydrochloride beads coated with an aqueous dispersion of ethylcellulose, theophylline beads coated with an aqueous dispersion of polymethacrylates, and theophylline beads coated with a mixture of an aqueous dispersion of ethylcellulose and polymethacrylates were prepared using Avicel® PH200 (MCC) or freeze-dried cushioning beads as filler-binder.

The two different filler systems, namely MCC with a mean particle size of 200 μm and the freeze-dried cushioning beads (14-20 mesh cut, 850-1400 μm), were used to study the effect of the filler particle size on the segregation propensity of the biologically active ingredient-loaded beads (14-20 mesh cut). The cushioning beads were expected to minimize the segregation propensity due to size differences, which is reflected in the content uniformity and weight variation of the tablets. Moreover, the cushioning beads should deform more readily than the biologically active ingredient-loaded beads, so that fracture of the membrane is minimized.

- 154 -

1. Compaction of Biologically Active Ingredient-loaded Beads in Different Different Filler Systems

The compaction profiles of the 25% and 50% propranolol hydrochloride beads (coated with ethylcellulose from an organic solvent) in MCC and freeze-dried cushioning beads can be found in Figure 33. Profiles for 12.5% and 25% phenylpropanolamine (PPA-HCl) combined with cushioning beads or MCC can be seen in Figure 34. Compaction profiles for beads containing 12.5% or 25% theophylline RD010 (coated with methacrylate copolymers) combined with cushioning beads or MCC can be seen in Figure 35. A single compaction profile for 12.5% theophylline RD011 (coated with a mixture of Aquacoat® and methacrylate copolymers) in cushioning beads was generated and is presented in Figure 36.

Increasing compaction pressure increased the tensile strengths of tablets. On the other hand, increasing the percentage of biologically active ingredient-loaded beads produced compacts of lower tensile strengths, due to a reduction in the amount of compactible filler-matrix.

When MCC was used as the filler-binder, segregation was visually observed in the tablet feed frame where the biologically active ingredient-loaded beads appeared to be separating from the powder mix as a function of time. Since in the design of the compaction study, tablets at lower compression pressures were collected first, the sifting of MCC throughout the inter-beads void spaces produced tablets which were initially more rich in MCC, while tablets collected towards the end of the compaction study (at high compression pressures) contained higher levels of biologically active ingredient-loaded beads.

This segregation confounded the tensile strength/compression pressure measurements, as can be seen in Figure 35, where the tablets compressed at a pressure of 603.1 Kg/cm^2 exhibited lower tensile strengths than those compressed at 467.5 Kg/cm^2. However, when cushioning beads were used as the filler-binder, the content uniformity was consistent throughout the run and no segregation was observed.

2.   Content Uniformity and Weight
      Variation Study

The actual amount of the biologically active ingredient analyzed in the different coated-bead systems studied were 66.0% (1.0) for the propranolol hydrochloride beads, 31.0% (7.7) for the PPA-HCl beads, 66.8% (2.8) for the theophylline RD010 beads, and 59.8% (1.9) for the theophylline RD011 beads.

The content uniformity and weight variation of the compacts produced as a function of compression pressures for propranolol hydrochloride, phenylpropanolamine hydrochloride, theophylline RD010 and theophylline RD011 can be seen Tables 23-26 below, respectively.

In general, weight variation was greater when MCC was used as the filler binder in the formulations containing PPA-HCl and theophylline. As seen in Table 24 below, tablets produced from the formulations containing 12.5% and 25% PPA-HCl in cushioning beads (8.0% croscarmellose sodium in MCC) had a smaller C.V.% (0.8% and 0.4%, respectively) than those produced from the formulation containing 12.5% PPA-HCl in MCC (C.V.% = 1.8). This difference was even more pronounced in the compacts containing theophylline RD010 beads (Table 25), where the C.V. was 1.4% for the 12.5% RD010 in cushioning beads and 11.1% for MCC.

This variation in weight encountered when MCC was used as the filler, can be attributed to the segregation occurring due to particle size differences. Whereas MCC has an average particle size of 200 μm, this is significantly smaller than the biologically active ingredient-loaded beads (850-1400 μm).

TABLE 23

25% Propranolol Hydrochloride Beads/75% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
182.7	830.3 (1.8)*	133.5 (2.8)	137.0 (1.8)
223.3	846.7 (0.7)	139.3 (1.2)	139.7 (0.7)
264.0	820.3 (1.9)	135.4 (3.9)	135.4 (1.9)
Average (C.V.%)	832.4 (1.9)	136.1 (3.1)	137.4 (1.9)
50% Propranolol Hydrochloride Beads/50% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
196.2	826.0 (0.7)	274.5 (4.3)	272.6 (0.7)
236.9	817.0 (2.6)	270.3 (6.2)	269.9 (2.6)
277.6	770.7 (1.7)	268.9 (1.0)	254.3 (1.7)
Average (C.V.%)	804.6 (3.6)	274.5 (4.3)	265.5 (3.6)
25% Propranolol Hydrochloride Beads/75% Avicel® PH200			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
155.5	770.7 (0.8)	90.3 (6.9)	127.2 (0.8)
223.3	771.3 (2.0)	107.1 (13.6)	127.3 (2.0)
304.7	798.7 (1.6)	138.7 (9.4)	131.8 (1.6)
Average (C.V.%)	780.2 (2.2)	112.0 (21.0)	128.7 (2.2)
50% Propranolol Hydrochloride Beads/50% Avicel® PH200			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
169.1	840.3 (1.8)	275.9 (6.0)	277.3 (1.8)
209.8	849.7 (1.6)	294.0 (8.1)	280.4 (1.6)
291.1	871.7 (1.1)	333.0 (5.5)	287.7 (1.1)
Average (C.V.%)	853.9 (2.1)	301.0 (10.2)	281.8 (2.1)

* Relative standard deviation

- 158 -

TABLE 24

25% Propranolol Hydrochloride Beads/ 87.5% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of PPA-HCl Present (mg)	Theoretical Amount of PPA-HC Present (mg)
169.1	1295.3 (0.4)*	45.48 (4.1)	50.2 (0.4)
223.3	1293.0 (0.4)	49.4 (1.5)	50.1 (0.4)
331.8	1291.0 (0.4)	50.2 (7.8)	50.0 (0.4)
Average (C.V.%)	1293.1 (0.4)	48.3 (5.0)	50.1 (0.4)
12.5% Phenylpropranolol Hydrochloride Beads/ 87.5% Avicel® PH200			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of PPA-HCl Present (mg)	Theoretical Amount of PPA-HCl Present (mg)
94.5	1465.7 (1.0)	59.3 (7.3)	56.8 (1.0)
162.3	1426.7 (2.4)	61.8 (8.5)	55.3 (2.4)
250.5	1459.0 (0.8)	49.6 (18.4)	56.5 (0.8)
Average (C.V.%)	1450.4 (1.8)	56.9 (14.0)	56.2 (1.8)
25% Phenylpropranolol Hydrochloride Beads/ 75% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
169.1	791.3 (0.4)	64.1 (9.3)	61.3 (0.4)
223.3	778.3 (1.0)	61.4 (5.4)	60.3 (1.0)
331.8	775.0 (0.7)	64.8 (7.7)	60.1 (0.7)
Average (C.V.%)	776.7 (0.8)	63.4 (7.1)	60.2 (0.8)

* Relative standard deviation

TABLE 25

12.5% Theophylline RD010 Beads/87.5% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of PPA-HCl Present (mg)	Theoretical Amount of PPA-HC Present (mg)
223.3	1212.0 (0.6)*	101.1 (3.6)	101.2 (0.6)
331.8	1208.7 (0.2)	102.1 (2.3)	100.9 (0.2)
467.5	1237.0 (1.3)	98.1 (6.6)	103.3 (1.3)
Average (C.V.%)	1219.2 (1.4)	100.4 (4.3)	101.8 (1.4)
25% Theophylline RD010 Beads/75% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of PPA-HCl Present (mg)	Theoretical Amount of PPA-HCl Present (mg)
223.3	1177.3 (0.2)	208.3 (0.4)	196.6 (0.2)
331.8	1164.0 (0.4)	204.9 (2.2)	194.4 (0.4)
467.5	1149.0 (0.3)	189.8 (2.1)	191.9 (0.3)
603.1	1158.0 (0.7)	201.8 (4.6)	193.4 (0.7)
Average (C.V.%)	1162.1 (1.0)	201.2 (4.3)	194.1 (1.0)
25% Theophylline RD010 Beads/75% Avicel® PH200			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Propranolol Present (mg)	Theoretical Amount of Propranolol Present (mg)
223.3	1124.0 (1.3)	169.8 (9.3)	187.7 (1.3)
331.8	1128.3 (1.4)	170.9 (5.0)	188.4 (0.3)
467.5	1108.3 (1.4)	175.1 (9.3)	185.1 (1.4)
603.1	1108.3 (1.4)	333.8 (1.3)	235.7 (1.4)
Average (C.V.%)	1192.9 (11.1)	212.4 (34.8)	199.2 (11.1)

* Relative standard deviation

- 160 -

TABLE 26

12.5% Theophylline RD010 Beads/87.5% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of PPA-HCl Present (mg)	Theoretical Amount of PPA-HC Present (mg)
223.3	1320.0 (0.8)*	95.9 (1.5)	98.7 (0.8)
331.8	1302.7 (0.1)	96.7 (5.2)	97.4 (0.1)
467.5	1285.0 (0.9)	100.1 (5.4)	96.1 (0.9)
603.1	1234.3 (0.3)	94.3 (4.0)	92.3 (0.3)
Average (C.V.%)	1219.2 (1.4)	100.4 (4.3)	96.1 (2.7)

* Relative standard deviation

The content uniformity of the different biologically active ingredients was much better when the freeze-dried cushioning beads were used as the filler system. For the compacts containing propranolol hydrochloride beads in cushioning beads, the C.V.% in the biologically active ingredient content was less than 5.0%, whereas those in MCC, the C.V.% in the biologically active ingredient content was 21.0% and 10.2% for the 25% and 50% propranolol loads, respectively (Table 23). Moreover, it is quite evident that as the compression pressure is increased in formulations containing MCC (tablets produced at later time points), the compacts became richer in propranolol.

The same trend was observed in the content uniformity measurements of PPA-HCl and theophylline RD010. For compacts produced using PPA-HCl in MCC, the C.V.% in the biologically active ingredient content was 14.0% for the formulation containing 12.5% PPA-HCl. This was much lower for the formulations containing 12.5% and 25% PPA-HCl in cushioning beads, where the C.V.% was only 5.0% and 7.1%, respectively (Table 24). For the formulation containing 25% theophylline RD010 in MCC, the C.V.% in the biologically active ingredient content was extremely high (34.8%), with the compacts produced at higher compression pressures (at later time points) exhibiting an increasing amount of the biologically active ingredient content (Table 25). The content uniformity for their cushioning beads counterparts was only 4.3% for both of the 12.5% and 25% theophylline in cushioning beads. Moreover, for the theophylline RD010 in cushioning beads, the C.V.% are acceptable 4.3% (Table 26).

- 162 -

3.   Effect of Compression Pressure on the Release of Biologically Active Ingredient from Tablets

The effect of compression pressure on the release of biologically active ingredient from formulations composed of 25% and 50% propranolol in cushioning beads and 12.5% and 25% phenylpropanolamine in cushioning beads is depicted in Figures 37-40, respectively. Dose dumping even at low compression pressure is obvious when comparing the dissolution profiles of the uncompacted and compacted beads. Increasing the load of the propranolol beads from 25% to 50% (Figure 41) and PPA-HCl beads from 12.5% to 25% (Figure 42) was associated with an increase in the release profiles. This increase can be attributed to the fact that as the percentage of the biologically active ingredient-loaded beads is increased, fewer cushioning beads were available to protect the membrane around the biologically active ingredient-loaded beads from fracturing. Figures 43 and 44 depict the effect of increasing compression pressure on the release of propranolol and PPA-HCl from the formulations containing 25% propranolol hydrochloride and 12.5% PPA-HCl in MCC, respectively. Higher compression pressures were associated with faster release profiles and more dose dumping, due to increased fracturing of the coated beads. The ability of the different filler systems utilized to protect the propranolol beads and PPA-HCl beads from fracturing at approximately similar compression pressures can be seen in Figures 45 and 46, respectively. MCC seems to provide a slightly better cushioning effect for the biologically active ingredient-loaded beads than the freeze-dried cushioning beads. However, in all of the compressed

propranolol bead and PPA-HCl formulations, severe dose
dumping occurred regardless of the pressure used to
form the compacts. Examining the photomicrograph of
the fractured tablet containing 25% propranolol in

5   75% cushioning beads produced at a compression
pressure of 264.0 Kg/cm^2, and that of the fractured
tablet containing 12.5% PPA-HCl in 87.5% cushioning
beads produced at a compression pressure of
331.8 Kg/cm^2 revealed that the beads present in the

10   interior part of the tablet matrix do not appear to
deform, which suggests that the dose dumping is due to
the cracking of the ethylcellulose coating, rather
than the fracturing of the beads themselves. The
scanning electron micrographs (55X) of representative

15   propranolol hydrochloride beads and PPA-HCl beads
obtained from the interior part of the tablet matrix
revealed severe cracking of the ethylcellulose
membrane coating. Ethylcellulose is a very brittle
material, and its films were reported to exhibit

20   massive fracture under compression regardless of the
plasticizer or other additives used (Béchard et al,
supra).

The effect of compression pressure on the release
of theophylline from formulations composed of

25   12.5% and 25% theophylline RD010 beads in cushioning
beads is depicted in Figures 47 and 48, respectively.
At both bead load levels, increasing the compression
pressure resulted in an increase in the release of the
biologically active ingredient as a function of time,

30   due to more cracking of the membrane-coated beads.
When comparing the dissolution profiles of the
compacted tablets to that of the uncompacted
theophylline RD010 beads, dose dumping is not as
significant as that encountered with

35   ethylcellulose-coated beads containing propranolol and

- 164 -

PPA-HCl. However, more change in the release profiles
is encountered with the 25% theophylline
RD010/cushioning beads profiles than the
12.5% counterparts. Increasing the theophylline RD010

5   beads load from 12.5% to 25% (Figure 49) was
associated with an increase in the release profiles of
tablets compacted at similar compression pressure of
331.8 Kg/cm^2, due to less cushioning beads available to
protect the biologically active ingredient-loaded

10   beads from fracturing. Figure 50 depicts the effect
of increasing the compression pressure on the release
of theophylline from the formulation containing
25% theophylline RD010 in MCC. Higher compression
pressures are associated with a slightly faster

15   release profiles and more dose dumping. The most
severe dose dumping associated with that formulation
compressed at a 603.1 Kg/cm^2 can be explained by the
fact that due to segregation encountered with the use
of MCC as the filler-binder, the tablets compacted at

20   high compression pressures (at later time points of
the compaction study) showed poor content uniformity
(higher amount of biologically active
ingredient-loaded beads and less amount of MCC).
Thus, the amount of MCC available to protect the

25   biologically active ingredient-loaded beads was
reduced. The ability of the different filler systems
utilized to protect the theophylline RD010 beads from
fracturing at similar compression pressures is seen in
Figures 51 and 52. At a compression pressure of

30   331.8 Kg/cm^2 (Figure 51), MCC provided a slightly
better cushioning effect for the theophylline RD010
beads than the freeze-dried cushioning beads. This is
reflected in the slower release profiles from the
formulation containing MCC when compared to the

35   formulation containing cushioning beads as the filler

system.   However, at a compression pressure of
603.1 Kg/cm^2 (Figure 52), the cushioning beads
protected the theophylline RD010 beads better than
MCC. This is because at higher compression pressure,
the theophylline RD010/MCC had a content uniformity
problem with a lower amount of MCC present. Thus, the
effect of both filler systems studied on protecting
the integrity of the theophylline RD010 beads is not
conclusive, since it is confounded by segregation
problems. In all of the theophylline RD010/cushioning
beads release profiles, regardless of the compression
pressure used to form the compacts, dose dumping was
not significant. The amount of theophylline released
from the tablets containing 12.5% and 25% theophylline
RD010 loads in cushioning beads relative to the
uncompacted theophylline RD010 is presented in
Tables 27 and 28 below, respectively. Examining the
photomicrograph of the fractured tablet containing
25% theophylline RD010 in 75% cushioning beads
produced at a compression pressure of 467.5 Kg/cm^2
reveals that the theophylline RD010 beads present in
the interior part of the tablet matrix remained
intact. However, the beads present at the surface
were damaged severely. The increase in the
biologically active ingredient release with higher
compression pressure can be attributed to the fact
that at higher pressures, the tablet thickness is
reduced, resulting in higher surface area/volume
ratio. Thus, chances of the beads getting exposed to
the surface where the damage is occurring is greater.
These results suggest that the films formed using the
methacrylate copolymers can withstand the stresses of
compaction with minimal change in the release profile,
which is mainly attributed to the cracking of the
beads exposed to the surface. Polymethacrylates film

coatings are flexible enough and can withstand the
mechanical stresses of compression so that the release
patterns from compressed or uncompressed beads are
similar (Lehmann et al *supra*, Juslin et al, *supra*; and
5   Haubitz et al, *supra*).

Table 27

Time (Hr)	Uncompacted RD010 Beads (% Released)	Comp. Press, 223.3 Kg/cm² (% Released)	Comp. Press, 331.8 Kg/cm² (% Released)	Comp. Press, 467.5 Kg/cm² (% Released)
0	0.0	0.0	0.0	0.0
0.5	5.1	10.7	24.2	31.2
1	14.4	19.8	32.8	42.4
1.5	24.8	28.8	40.7	50.6
2	35.3	37.2	47.0	57.8
3	50.5	50.6	58.0	68.2
4	64.7	63.3	68.3	76.5
5	74.2	72.4	74.9	82.9
6	1.6	79.6	78.9	86.2
7	87.4	85.6	83.5	89.8
8	91.7	90.1	91.7	94.4
9	94.6	93.5	95.0	96.6
10	96.8	96.1	97.2	98.1
11	99.4	99.1	98.6	99.7
12	100.0	100.0	100.0	100.0

TABLE 28

Time (Hr)	Uncompacted RD010 Beads (% Released)	Comp. Press, 223.3 Kg/cm² (% Released)	Comp. Press, 331.8 Kg/cm² (% Released)	Comp. Press, 467.5 Kg/cm² (% Released)	Comp. Press, 603.1 Kg/cm² (% Released)
0	0.0	0.0	0.0	0.0	0.0
0.5	8.3	34.8	42.4	45.6	50.8
1	19.1	45.9	52.9	57.0	62.4
1.5	28.6	53.2	60.0	64.0	69.9
2	37.4	59.0	65.2	69.4	75.6
3	52.7	68.4	73.5	78.1	84.1
4	65.1	75.7	79.8	84.3	89.5
5	75.3	81.3	84.7	88.9	93.5
6	83.5	85.9	88.5	92.4	95.9
7	90.3	89.7	91.6	94.8	97.2
8	95.6	92.8	94.4	96.5	98.2
9	99.8	95.5	96.6	98.3	99.2
10	98.9	97.4	98.2	99.1	99.7
11	98.8	98.7	99.2	100.0	100.0
12	100.0	100.0	100.0	100.0	100.0

- 168 -

Similar results were obtained with the theophylline RD011 beads coated with a mixture of polymethacrylates and ethylcellulose aqueous dispersions. Increasing the compression pressure for the formulation containing 12.5% theophylline RD011 in cushioning beads resulted in a minor increase in the percent of the biologically active ingredient releases as a function of time (Figure 53). The amount of theophylline released from those tablets relative to the uncompacted theophylline RD011 beads is present in Table 29 below. Examining the photomicrograph of the fractured tablet containing 12.5% theophylline RD010 in 87.5% cushioning beads produced at a compression pressure of 467.5 Kg/cm^2 reveals that the theophylline RD011 beads present in the interior part of the tablet matrix remained intact. However, the beads present at the surface were damaged severely.

TABLE 29

Time (Hr)	Uncompacted RD011 Beads (% Released)	Comp. Press, 223.3 Kg/cm^2 (% Released)	Comp. Press, 331.8 Kg/cm^2 (% Released)	Comp. Press, 467.5 Kg/cm^2 (% Released)	Comp. Press, 603.1 Kg/cm^2 (% Released)
0	0.0	0.0	0.0	0.0	0.0
0.5	14.2	32.1	35.0	40.9	49.7
1	41.4	57.6	62.9	64.2	75.3
1.5	57.3	70.8	76.0	75.8	86.4
2	68.3	79.5	84.3	82.9	92.6
3	82.6	89.9	93.0	90.7	97.4
4	90.1	94.5	96.7	94.1	98.3
5	94.4	97.1	97.9	96.4	98.4
6	96.5	98.8	98.5	97.9	98.4
7	97.8	99.5	98.9	98.7	98.4
8	98.8	99.8	99.2	99.2	98.5
9	99.3	99.8	99.3	99.6	98.6
10	100.0	100.0	99.3	99.9	98.9
11	100.0	100.0	100.0	99.9	100.0
12	100.0	100.0	100.0	100.0	100.0

III. Conclusions

The mixing and compaction of the different biologically active ingredient-loaded beads with Avicel® PH200 (MCC) was associated with more significant weight variation and content uniformity problems than when the freeze-dried cushioning beads were used as the filler binder. This is attributed to the segregation due to size differences between the biologically active ingredient-loaded beads (850-1400 µm) and MCC (200 µm). When the freeze-dried cushioning beads of 14-20 mesh cut was used, segregation was minimal.

The freeze-dried cushioning beads, when mixed and compacted with the theophylline biologically active ingredient-loaded beads coated with polymethacrylate copolymer (RD010) and a mixture of polymethacrylate copolymer and ethylcellulose from aqueous dispersions

(RD011), were able to cushion the biologically active ingredient-loaded beads, and minimize dose dumping. The change in the release profiles of the uncompacted and compacted theophylline beads can be attributed to the inevitable fracturing of the beads occurring at the surface. However, dose dumping from tablets compressed with propranolol beads coated with ethylcellulose from organic solvent and phenylpropanolamine hydrochloride beads coated with an aqueous dispersion of ethylcellulose was pronounced at all loading levels and compression forces. This is because ethylcellulose films are very brittle, regardless of the plasticizers added. Polymethacrylate copolymers are much more flexible, and can withstand the mechanical stresses of the compaction process.

Increasing the compression pressure resulted in a slight increase in the dissolution profile of theophylline beads (both RD010 and RD011) compressed with the freeze-dried beads. This increase is due to the fact that with an increase in compression pressure, tablet thickness decreases, resulting in greater chance of exposing the theophylline beads to the surface where beads damage is prone to occur. Whereas the photomicrographs of the compacted beads revealed severe damage of the theophylline beads present at the surface, beads present in the interior tablet matrix remained intact.

Increasing the thickness of the compacts is expected to reduce the percentage of the theophylline beads (RD010 or RD011) experiencing damage at the surface. Thick compacts should not impose any problem if the tablet is to be dispersed in water prior to dose administration.

- 171 -

A biologically active ingredient load of 25% of theophylline in cushioning beads appears to be a reasonable figure to be used in later studies to manufacture the self-disintegrating tablets intended to provide a sustained release aqueous suspension. This self-disintegrating tablet will contain 25% of both carbomer EX214 beads described in Example 1 above and the theophylline beads coated with polymethacrylate copolymer (RD010) and 75% of the freeze-dried cushioning beads described in Example 2 above.

EXAMPLE 4
Formulation and Manufacture of Tablets
for Instantaneous Preparation of Sustained
Release Suspensions

I.   Introduction

A water-dispersible tablet containing biologically active ingredient-loaded beads, a disintegrant, and a swellable material capable of generating a high viscosity when coming in contact with water is described in this Example. Biologically active ingredient-loaded membrane-coated beads, consisting of theophylline produced by extrusion-spheronization and coated with polymethacrylate copolymer as described in Example 3, and capable of withstanding the mechanical stresses of compression, were mixed with the carbomer/MCC beads, described in Example 1, and the freeze-dried cushioning beads containing 8.0% croscarmellose in MCC described in Example 2 above. These three components were compressed to form a tablet, which when dispersed in water, is expected to disintegrate rapidly to release the theophylline beads together with the carbomer beads, resulting in a homogenous suspension.

- 172 -

II.   Experiments

A.   Materials

Theophylline beads (RD010) were supplied by Niro-Aeromatic (Columbia, MD). The theophylline beads (60% biologically active ingredient content) were produced by extrusion-spheronization. The sustained action was imparted by coating with a 6.0% (w/w) polymethacrylic acid aqueous polymeric dispersion. The coating was composed of 48% amminomethacrylate copolymer and 9.5% methacrylic acid copolymer plasticized with 9.5% (w/w) triethyl citrate. A 2.0% (w/w) overcoat was also applied.

The carbomer beads consisted of 30% (w/w) neutralized carbomer (Carbopol® EX214) in MCC were produced, as described in Example 1 above, by extrusion-spheronization using a 50% hydroalcoholic solution as the wet massing agent.

The cushioning beads, composed of 8.0% croscarmellose sodium in MCC, were produced by extrusion-spheronization as described in Example 2 above, using water as the wet massing agent, followed by freeze-drying.

III. Methods

A.   Production of Tablets

A 500 g batch containing 8.3% Theophylline (RD010) biologically active ingredient-loaded membrane-coated beads (14-20 mesh cut), 16.7% carbomer beads (20-30 mesh cut) and 75% freeze-dried cushioning beads (14-20 mesh cut) was blended for 10 min in a 2.0 quart twin-shell blender. Tablets were compressed on a single station of an instrumented rotary tablet press (Stokes RB-2) utilizing a 1.58 mm flat-faced beveled-edge punches. The instrumentation for the measurement of compression force has been previously

described by Salpekar et al, *supra*. The angular separation between filling and compression was 180°C. Approximately twenty tablets were collected at compression pressures of 223.3, 331.8, 603.1 and 467.5 Kg/cm^2. After 24 hrs of storage, the thickness of 5 individual tablets at each compression force was determined using a digital micrometer. The crushing strength (P) of the tablets was determined by diametral loading in a standard motorized tester. The value used for P was the mean of five crushing strength determinations of tablets at each compression pressure. Tablet tensile strength (σ) in Kg/cm^2 was calculated using Equation (1) above. Compaction profiles were generated consisting of the different tablets tensile strengths as a function of compression pressures utilized in their production.

B.   Determination of the Content
       Uniformity of the Compacts

Three samples of the tablets produced at each compression pressure were randomly selected and analyzed for the theophylline content. Each tablet was weighed and transferred separately to a 100 ml volumetric flask containing about 70 ml of distilled water. Each flask was placed in a mechanical shaker for 24 hrs to allow the biologically active ingredient to be released. A 24 hr period was adequate for complete release of the biologically active ingredient, as determined from the dissolution profile of uncompacted beads as described in Example 3, where the asymptote was reached at 10 hrs. Dilution to volume was followed by shaking each flask to ensure uniform mixing. A portion of the solution was centrifuged at 1000 RPM for about 10 min to obtain a clear solution. 5.0 ml of the clear supernatant was

transferred to a 100 ml volumetric flask, and was diluted to volume with distilled water and mixed. The content was determined spectrophotometrically at a wavelength of 271 nm using the previously constructed standard curve.

C.   Dissolution of the Bead
Mixture and its Compacts

Dissolution studies were performed using the USP XXIII apparatus 2 at a paddle speed of 50 RPM. The release profiles of theophylline from the uncompacted bead blend and for tablets at the different compression pressures were evaluated in triplicate to study the effect of compression on the release kinetics of the biologically active ingredient. The dissolution medium consisted of 900 ml of degassed distilled water maintained at 37°C. The dissolution apparatus was calibrated using USP prednisone and salicylic acid calibrator tablets. Direct ultraviolet detection at 271 nm was used to assess the biologically active ingredient concentration in the dissolution medium. Dissolution medium was continuously pumped through 0.1 cm flow cells cuvettes by a peristaltic pump.

D.   Photomicroscopy of Tablet Compacts

Magnified photographs for the fractured tablets produced at a compression pressure of 467.5 Kg/cm^2 were taken at a magnification of 19X to check for any fracturing of the biologically active ingredient-loaded beads and carbomer beads occurring inside the tablet matrix as a result of the compaction process. Moreover, surface pictures of intact tablets were taken at a similar magnification to examine for any fracturing of the beads exposed to the surface.

A Wild Leipz microscope (Wild Leipz USA Inc.,
Rockleigh, NJ) connected to Sony Video Printer (Model
UP5000, Sony Corp., Tokyo, Japan) was used.

E.   Evaluation of the Suspension

The ability of the tablet containing the
biologically active ingredient-loaded beads, carbomer
beads and cushioning beads to form a suspension was
evaluated by dispersing 3 tablets (average weight of
each 1375.5 g) in a beaker containing 100 ml of
distilled water. The beaker was stirred for 0.5, 1.0
or 1.5 min at a fixed speed (level 7) on a Nuova II
Stir Plate. The experiment was repeated at three
different stirring times, after which the dispersion
was transferred to a 100 ml graduated cylinder and
after 5.0 sec were allowed for settling to occur,
photographs of the settling suspension were taken. The
three tablets provided a 687.5 mg of the carbomer
beads (30% (w/w) carbomer) which when dispersed in
100 ml of water provide a final concentration of
carbomer of 0.2%. A concentration of 0.175-0.2% is
shown in Example 3 to provide a good suspending
ability.

IV.   Results and Discussion

Water-dispersible tablets containing beads which
have been coated by a rate controlling membrane to
sustain biologically active ingredient delivery, a
swellable material able to rapidly generate viscosity
when coming in contact with water, and a filler system
capable of protecting the membrane controlling the
biologically active ingredient release, as well as
improving content uniformity, were manufactured.
Compaction properties of the mixture, content
uniformity and weight variation of the tablets, and

the effect of compression pressure on the release of
the biologically active ingredient from the tablets
were evaluated.

A.   Compaction Study

The compaction profiles of the blend containing
theophylline RD010 beads, carbomer beads and
cushioning beads and that containing 25% RD010 in
cushioning beads (see Example 2) is depicted in
Figure 54.   Increasing the compression pressure
increased the tensile strengths of tablets. Although
the level of the cushioning beads in both formulations
was 75%, the increase in the tensile strength was much
more pronounced with the formulation containing the
carbomer beads.   This could be attributed to the
hygroscopic nature of carbomer, which might have
absorbed some moisture from the atmosphere during
blending and tabletting, resulting in an additional
adhesive power enhancing the tablet tensile strength.

B.   Content Uniformity and Weight Variation Study

The actual amount of the biologically active
ingredient detected in the theophylline RD010
coated-beads was 66.8% (±2.8). The content uniformity
and weight variation of the compacts produced as a
function of compression pressures are seen Table 30
below.   Weight variation was 4.3% and the content
uniformity was 4.9%. No segregation was evident, as
reflected in the tight content uniformity achieved.

TABLE 30

8.3% Theophylline RD010 Beads and 16.7% Carbomer Beads in 75% Cushioning Beads			
Compression Force (Kg/cm^2)	Tablet Weight (mg) (n=3)	Actual Amount of Theophylline Present (mg)	Theoretical Amount of Theophylline Present (mg)
223.3	1463.7 (1.5)	78.4 (6.4)	80.7 (1.5)
331.8	1381.0 (0.7)	74.5 (1.2)	76.1 (0.7)
467.5	1335.3 (0.4)	75.4 (6.2)	73.6 (0.4)
603.1	1322.0 (0.6)	74.6 (5.0)	72.9 (0.6)
Average (C.V. %)	1375.5 (4.3)	75.7 (4.9)	75.8 (4.3)

* Relative standard deviation

C.   Effect of Compression Pressure on
      the Release of Biologically Active
      Ingredient from Tablets

The effect of compression pressure on the release
5   of theophylline from the uncompacted blend and the
compressed tablets is depicted in Figure 55. Higher
compression pressures were associated with slightly
faster release profiles. This is because at higher
compression pressures, more cracking of the
10   membrane-coated beads occurred, which can be
attributed to the fact that at higher pressures, the
tablet thickness is reduced, resulting in higher
surface area/volume ratio. Thus, chances of the beads
getting exposed to the surface where the damage is
15   occurring is greater. Examining the photomicrograph
of the fractured tablet reveals that the theophylline
RD010 beads and carbomer beads present in the interior
part of the tablet matrix remained intact, whereas the
cushioning beads deformed and surrounded the other

- 178 -

beads so that the tablet is held together by excipient-excipient contact. The surface photomicrograph of the intact tablet reveals a severe damage of the theophylline RD010 beads. The freeze-dried cushioning beads, when mixed and compacted with the theophylline biologically active ingredient-loaded beads coated with polymethacrylate copolymer (RD010) and carbomer beads, were able to cushion the biologically active ingredient-loaded beads and minimize dose dumping.

D.   Evaluation of the Suspension

A stirring time of 0.5 min was associated with a relatively quick sedimentation rate of the beads in the formed suspension. However, a stirring time of 1.0 min resulted in a uniform suspension where the settling of the beads was relatively slow, a time sufficient to allow the patient to swallow the dose before appreciable sedimentation takes place. Stirring for 1.5 min produced a very stable suspension where the beads did not show any sign of settling at all. The decrease in settling of beads as a function of stirring time is attributed to the increase in the release of viscosity enhancer from the carbomer beads with time.

IV.   Conclusions

A novel approach for the oral administration of multi-particulates is to suspend them in a liquid vehicle which spontaneously forms a suspension, when a tablet is reconstituted with water by the patient just prior to administration.

The tablets produced in this Example had a good tensile strength, which can be attributed to the excipient-excipient contact formed by the initial

fragmentation, and plastic deformation of the freeze-dried cushioning beads, together with the adhesive action of the carbomer beads. The carbomer beads, being hygroscopic in nature, tend to absorb moisture from the atmosphere, resulting in an additional binding power. The disintegration of the tablets was not impeded due to this additional adhesive power of the carbomer beads.

The content uniformity and weight variation were less than 5.0% because of the absence of segregation, due to similar sizes of the beads and the filler system.

The freeze-dried cushioning beads and carbomer beads, when mixed and compacted with the theophylline biologically active ingredient-loaded beads coated with polymethacrylate copolymer (RD010) were able to cushion the biologically active ingredient-loaded beads and minimize dose dumping. Increasing the compression pressure resulted in a slight increase in the dissolution profile of theophylline beads. This increase is due to the fact that with an increase in compression pressure, tablet thickness decreases, resulting in a greater chance of exposing the theophylline beads to the surface where beads damage is prone to occur. Whereas the photomicrographs of the compacted beads revealed severe damage of the theophylline beads present at the surface, beads present in the interior tablet matrix appear to remain intact.

The tablets were able to generate a homogenous suspension and to minimize the settling of the biologically active ingredient-loaded beads for a time sufficient for the dispersed dose to be administered.

- 180 -

SUMMARY AND CONCLUSIONS

Multi-unit dosage forms of controlled release have been formulated with coated particles for many years, but in most cases have been filled into hard gelatin capsules. Such preparations present numerous disadvantages: The capsules themselves are relatively expensive, the bulk density inside the capsule is low so that a larger volume is needed for high doses, and the dose cannot be divided. Tablets can be produced less expensively and can be divided without significant influence on the biologically active ingredient release, which is controlled after disintegration of the tablet by the intact coated particles. Moreover, the concept of tabletting coated biologically active ingredient particles prevents criminal tampering with the product.

Compaction of beads posed problems for pharmaceutical formulators. If the beads have been coated by a rate controlling membrane to sustain biologically active ingredient delivery, cracking of the membrane will cause the delivery system to change the rate of biologically active ingredient delivery or completely dose dump. Thus, it is of great interest to investigate methods by which cracking can be prevented.

Conventional highly compactible fillers, such as MCC, can be mixed with biologically active ingredient-loaded beads and compressed to form tablets. However, due to particle size differences, segregation is encountered, resulting in weight variation and content uniformity problems. Granules produced by dry or wet granulation techniques having similar size to biologically active ingredient-loaded beads minimized segregation. However, dry or wet granulations of MCC-containing mixtures decreases

compactibility. Moreover, the use of large amounts of filler-binders or cushioning agents to prevent the cracking of the membrane-coated beads can result in large tablets which are difficult to swallow.

An alternative approach for the oral administration of multi-particulates is to suspend them in a liquid vehicle to form a suspension or into a dry powder system or a tablet, which is to be reconstituted with water by the patient just prior to administration. These types of dosage forms overcome the above-mentioned problems, and are often preferred for infants, children, and elderly patients.

An aim of the present invention was to produce a water-dispersible tablet containing biologically active ingredient-loaded microparticles, a filler, and a swellable material capable of generating a high viscosity when dispersed in water. When coming in contact with water, the tablet disintegrated rapidly to surpass the opposite swelling effect caused by the viscosity enhancer. After the tablet has disintegrated in water, the viscosity enhancer swells, resulting in a homogenous suspension consisting of biologically active ingredient-loaded beads and other excipients. The distribution of the viscosity enhancer particles within the tablet is important because complete disintegration of the tablet has to take place before the swelling of the viscosity enhancer prevents the disintegration.

A systematic approach was used in the design of the self-disintegrating tablet for the formation of extemporaneous sustained release suspension. The first step was to screen different viscosity enhancers which exhibit quick hydration, and find one that increase the viscosity of the dispersion medium at a low concentration. Carbomer (Carbopol® EX214) was

chosen as the viscosity enhancer. This was followed
by processing the fine powder of the viscosity
enhancer into separate entities (beads) to allow the
tablet to disintegrate first, followed by the build-up
5   of viscosity. If powdered the viscosity enhancers
were used instead, the disintegration process would be
impeded, resulting in a voluminous tablet mass, which
is difficult to disintegrate.

The second step was to formulate cushioning beads
10   to act as a filler. The filler should have minimal
segregation propensity (similar size, density, and
shape), and should cushion the sustained-release
biologically active ingredient-loaded beads to prevent
dose dumping. It should preferably exhibit initial
15   fragmentation into primary powder particles, followed
by plastic deformation during the compaction with the
biologically active ingredient-loaded membrane-coated
millispheres. This is so because the filler should
not only fill the voids between the biologically
20   active ingredient-loaded beads, but also should
surround them so that the tablet is held together by
excipient-excipient contact. The filler should
disintegrate rapidly to release the intact
biologically active ingredient-loaded beads, and
25   should have a minimal effect on biologically active
ingredient release kinetics. Freeze-drying of beads
provided a successful approach for cushioning beads
production.

The third step was to test the ability of the
30   cushioning beads to protect the coated biologically
active ingredient-loaded beads so that the release
profile of the biologically active ingredient is not
changed. Polymethacrylate copolymer coatings were
able withstand the mechanical stresses of compression
35   with minimal dose dumping.

The final step was to produce tablets intended to
be used for the instantaneous preparation of a
sustained release suspension. Biologically active
ingredient-loaded membrane-coated beads, consisting of
theophylline produced by extrusion-spheronization and
coated with polymethacrylate copolymer, carbomer/MCC
beads and freeze-dried cushioning beads were
compressed to form a tablet. When dispersed in water,
the tablet disintegrated quickly to release the intact
biologically active ingredient-loaded beads together
with the carbomer beads, resulting in a homogenous
suspension.

I.   Screening of Viscosity Enhancers
        and its Processing

        Standard viscosity enhancers could be
incorporated into such a tablet system to reduce
sedimentation or floating of the particles. Two
factors played a role in the choice of a viscosity
enhancer. The first was the concentration needed in
the final dispersed form to impart enough structure.
The second was the rate of viscosity build-up which
should be fast enough to provide adequate suspension
properties, yet should not interfere with the
disintegration of the tablet.

        The presence of the viscosity enhancer as fine
powder particles in a tablet matrix prevents the rapid
disintegration and subsequent dispersion of the
contents of the tablet. This is because the fine
powder of the viscosity enhancer tends to network with
each other, so that upon contact with water, the
networked polymer particles at the surface would
hydrate, preventing the further penetration of water
to the interior of the tablet and the disintegration
process is inhibited. The layering of the viscosity

- 184 -

enhancers onto placebo sugar spheres or extrusion-spheronization of the viscosity enhancer to form beads are among the various approaches attempted in the present invention to solve the problems of tablet disintegration and powder dispersion.

Among the various polymers evaluated for their rheological properties, carbomer (Carbopol® EX214) proved to be an ideal candidate, in terms of speed of hydration, presence of yield value and lowest concentration needed to achieve an optimal viscosity required to minimize the sedimentation rate of suspended particles.

The powder-layering of carbomer on the surface of sugar spheres was achieved by using the EX214 grade, which does not hydrate in alcohol together with an alcoholic PVP solution. Similar concentrations of the different grades of alcoholic PVP solutions (K29-32 and K90) produced beads with almost equivalent yield, percentage loading, and similar release profiles of carbomer. Increasing the concentration of PVP in the alcoholic binder solution increased the yield, and the percentage loading, but decreased the amount of carbomer released at the early time points.

Extrusion-spheronization of carbomer was achieved by using a hydroalcoholic granulating liquid to reduce the tackiness. This approach avoided the detrimental effects of ionic salts or pH modifiers on the ability of the polymer to build-up viscosity when hydrated. Increasing the water/alcohol ratio in the granulating solution decreased the amount of carbomer released as a function of time at the early time points. The size of the carbomer beads is of significant importance in determining the release profile of carbomer, indicating that dissolution-erosion type of release is involved, rather than disintegration.

- 185 -

Superdisintegrants were not able to increase the rate of carbomer released as a function of time.

Processing carbomer by extrusion-spheronization produced beads with faster release profiles and more carbomer loading than powder-layering. The beads containing 30% carbomer in MCC (Avicel® PH101) produced by extrusion-spheronization was selected as the swellable material to be included in the water-dispersible tablets to retard the sedimentation process.

II. Formulation of Cushioning Beads

Ideal inert "cushioning" beads intended to be used as diluent to be mixed with biologically active ingredient-loaded beads to prevent segregation, whether due to size or density, should have minimal segregation propensity (similar size, density, and shape) and should cushion the sustained-release biologically active ingredient-loaded pellets to prevent dose dumping. Freeze-drying of beads of different composition provided a successful approach for cushioning beads production.

Different materials, including disintegrants such as starch, superdisintegrants, such as croscarmellose sodium, crospovidone, and sodium starch glycolate, and hydrophilic materials, such as hydroxypropyl cellulose, can be incorporated to increase the water content of the extruded-spheronized beads. Superdisintegrants can be incorporated at much lower levels than regular disintegrants to increase the water content. Materials included in the granulating mixture to increase the water level should be efficient at low concentrations and should not cause the extrudate to be sticky, so that during spheronization, balling of the beads should not occur.

Hydroxypropyl cellulose, starch and sodium starch glycolate form viscous and sticky extrudates, which are difficult to spheronize.

Inert cushioning beads of different compressibilities, compactibilities and disintegration ability were produced by freeze-drying. The optimal granulating fluid level for the different formulations studied, as determined by image analysis based on the size and roundness of the fresh undried beads, was essential to investigate the effect of different formulation variables on the properties of the dried product.

The presence of high levels of MCC and different superdisintegrants, especially croscarmellose, generally increased the granulating fluid levels requirement, thus producing freeze-dried beads with higher porosities. Compactibility studies indicated that in the absence of croscarmellose, lactose-predominant formulations were more compactible than those predominant in MCC. A major interaction was observed between MCC and croscarmellose. In the presence of high levels of MCC in the formulation, croscarmellose-containing freeze-dried beads were the most compactible, producing the hardest tablets at the compression pressure ranges studied.

Compressibility studies revealed that formulations containing high levels of MCC exhibited lower yield values, thus were more compressible, than those formulations containing high levels of lactose. Superdisintegrants had no effect on the compressibility of beads, which could be attributed to the fact that compressibility measurements (yield values) were determined at compression forces which were higher than the ranges used in the compactibility

studies. Thus, the effect of the initial porosities
of the beads was diminished.

The yield values were very helpful in determining
the compaction mechanism of the freeze-dried beads.
Freeze-dried beads exhibited both plastic deformation
and brittle fracture.   The presence of plastic
deformation was detected by the presence of
strain-rate sensitivity to the compaction process when
the upper punch speed rate was varied.   Brittle
fracture component was detected in the relatively high
yield values associated with the freeze-dried beads.
The existence of both plastic deformation and brittle
fracture is desired in an ideal cushioning bead
system. This is so because when the cushioning beads,
mixed with biologically active ingredient-loaded
beads, are compacted, initial fragmentation into
progeny primary powder particles would not only fill
the voids between the biologically active
ingredient-loaded beads, but surround them. Plastic
deformation of the fine particles would then enhance
the excipient-excipient interaction, producing
stronger compacts.

Yield value measurements for different
bead-fractions were not able to depict the mechanism
of deformation, due to the narrow size-range of the
beads produced by extrusion-spheronization process.

Tray-drying of some batches produced beads with
smaller average diameters than those which were
freeze-dried. This is due to the shrinking associated
with tray-drying, which produced hard and dense beads.
The tray-dried beads were not able to form tablets of
any appreciable hardness when compacted.

III. Formulation of Fast Disintegrating Controlled
     Release Tablets from Coated Particles

The performance of the inert cushioning beads
produced by freeze-drying in minimizing the
segregation propensity and cushioning the biologically
active ingredient-loaded beads was practically
evaluated by mixing and compacting them with different
biologically active ingredient-loaded beads whose
action was sustained by different polymeric membranes.
Tablets containing propranolol beads coated with
ethylcellulose from organic solvent,
phenylpropanolamine hydrochloride beads coated with an
aqueous dispersion of ethylcellulose, theophylline
beads coated with an aqueous dispersion of
polymethacrylates, and theophylline beads coated with
a mixture of an aqueous dispersion of ethylcellulose
and polymethacrylates were prepared using MCC
(Avicel® PH200), or freeze-dried cushioning beads as
filler-binder.

The two different filler systems, namely
Avicel® PH200 with a mean particle size of 200 μm and
the freeze-dried cushioning beads (14-20 mesh cut,
850-1400 μm), were used to study the effect of the
filler particle size on the segregation propensity of
the biologically active ingredient-loaded beads
(14-20 mesh cut, 850-1400 μm). The cushioning beads
minimized the segregation propensity due to size
differences, as reflected in the content uniformity
and weight variation of the tablets. Moreover, the
cushioning beads deformed more readily than the
biologically active ingredient-loaded beads, so that
fracture of the membrane was minimized.

The mixing and compaction of the different
biologically active ingredient-loaded beads with MCC
(Avicel® PH200) was associated with more significant

weight variation and content uniformity problems than
when the freeze-dried cushioning beads containing
8.0% croscarmellose sodium in MCC was used as the
filler binder. This is attributed to the segregation
due to size differences between the biologically
active ingredient-loaded beads (14-20 mesh cut,
850-1400 μm) and MCC (200 μm). When the freeze-dried
cushioning beads of 14-20 mesh cut (850-1400 μm) were
used, segregation was minimal.

The freeze-dried cushioning beads, when mixed and
compacted with the theophylline biologically active
ingredient-loaded beads coated with polymethacrylate
copolymer (RD010) and a mixture of polymethacrylate
copolymer and ethylcellulose from aqueous dispersions
(RD011), were able to cushion the biologically active
ingredient-loaded beads and minimize dose dumping.
However, dose dumping with propranolol beads coated
with ethylcellulose from organic solvent and
phenylpropanolamine hydrochloride beads coated with an
aqueous dispersion of ethylcellulose was inevitable.
This is because ethylcellulose films are very brittle,
regardless of the plasticizers added.
Polymethacrylate copolymers are much flexible, and can
withstand the mechanical stresses of the compaction
process.

Increasing the compression pressure resulted in
a slight increase in the dissolution profile of
theophylline beads (both RD010 and RD011) compressed
with the freeze-dried beads. This increase is due to
the fact that with an increase in compression
pressure, tablet thickness decreases with a
corresponding increase in surface area/volume ratio,
resulting in a greater chance of exposing the
theophylline beads to the surface where beads damage
is prone to occur. Whereas the photomicrographs of

- 190 -

the compacted beads revealed severe damage of the theophylline beads present at the surface, beads present in the interior tablet matrix remained intact.

A biologically active ingredient load of 25% of theophylline in cushioning beads appeared to be a reasonable figure to be used to manufacture the self-disintegrating tablets intended to deliver sustained release aqueous suspension.

IV.   Formulation and Manufacture of Tablets for Extemporaneous Preparation of Sustained Release Suspension

Biologically active ingredient-loaded membrane-coated beads, consisting of theophylline produced by extrusion-spheronization and coated with polymethacrylate copolymer, capable of withstanding the mechanical stresses of compression, were mixed with the carbomer/MCC beads and freeze-dried cushioning beads containing 8.0% croscarmellose in MCC.   These three components were compressed to form a tablet which, when dispersed in water, disintegrated quickly to release the theophylline beads together with the carbomer beads, resulting in a homogenous suspension.

The tablets produced had a good tensile strength, which can be attributed to the excipient-excipient contact formed by the initial fragmentation and plastic deformation of the freeze-dried cushioning beads, together with the adhesive action of the carbomer beads. The carbomer beads, being hygroscopic in nature, absorbed moisture from the atmosphere, resulting in an additional binding power.   The disintegration of the tablets was not impeded, due to this additional adhesive power of the carbomer beads.

The content uniformity and weight variation were less than 5.0% because of the absence of segregation, due to similar sizes of the beads and the filler system.

The freeze-dried cushioning beads and carbomer beads when mixed and compacted with the theophylline biologically active ingredient-loaded beads coated with polymethacrylate copolymer (RD010) were able to cushion the biologically active ingredient-loaded beads, and minimize dose dumping. Increasing the compression pressure resulted in a slight increase in the dissolution profile of theophylline beads. This increase is due to the fact that with an increase in compression pressure, tablet thickness decreases, resulting in greater chance of exposing the theophylline beads to the surface where beads damage is prone to occur. Whereas the photomicrographs of the compacted beads revealed severe damage of the theophylline beads present at the surface, beads present in the interior tablet matrix remained intact.

The tablets were able to generate a homogenous suspension and to minimize the settling of the biologically active ingredient-loaded beads for a time sufficient for the dispersed dose to be administered.

The production of viscosity enhancers in the form of beads without incorporating additional materials which having detrimental effects on the functionality of the viscosity enhancer, together with the production of freeze-dried cushioning beads of microcrystalline cellulose are some of the unique features of the present invention.

While the invention has been described in detail, and with reference to specific embodiments thereof, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made

therein without departing from the spirit and scope thereof.

- 193 -

WHAT IS CLAIMED:

Claim (1). A cushioning bead comprising microcrystalline cellulose, wherein said cushioning bead is prepared by extrusion-spheronization, followed by freeze-drying.

Claim 2. The cushioning bead as claimed in Claim 1, wherein said microcrystalline cellulose is present in the cushioning bead in an amount of from about 20-100%.

Claim 3. The cushioning bead as claimed in Claim 2, wherein said microcrystalline cellulose is present in the cushioning bead in an amount of from about 60-95%.

Claim 4. The cushioning bead as claimed in Claim 1, wherein said cushioning bead additionally comprises a disintegrant.

Claim 5. The cushioning bead as claimed in Claim 4, wherein said disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, starch, and pregelatinized starch.

Claim 6. The cushioning bead as claimed in Claim 5, wherein said disintegrant is croscarmellose sodium.

Claim 7. The cushioning bead as claimed in Claim 4, wherein said disintegrant is present in the cushioning bead in an amount of from greater than 0-50%.

Claim 8. The cushioning bead as claimed in Claim 7, wherein said disintegrant is present in the cushioning bead in an amount of from about 5.0-40%.

Claim 9. The cushioning bead as claimed in Claim 4, wherein the ratio of microcrystalline cellulose to disintegrant is about 1:0-0.2:0.8.

- 194 -

Claim 10. The cushioning bead as claimed in Claim 9, wherein the ratio of microcrystalline cellulose to disintegrant is about 0.95:0.05-0.6:0.4.

Claim 11. The cushioning bead as claimed in Claim 4, wherein said cushioning bead additionally comprises a filler.

Claim 12. The cushioning bead as claimed in Claim 11, wherein said filler is a water-soluble filler selected from the group consisting of lactose and sorbitol.

Claim 13. The cushioning bead as claimed in Claim 11, wherein said filler is dibasic calcium phosphate.

Claim 14. The cushioning bead as claimed in Claim 11, wherein said filler is present in the cushioning bead in an amount of from greater than 0-80%.

Claim 15. The cushioning bead as claimed in Claim 14, wherein said filler is present in the cushioning bead in an amount of from greater than 0-50%.

Claim 16. A tablet comprising:

(i)   biologically active ingredient-loaded beads; and

(ii) cushioning beads comprising microcrystalline cellulose, wherein said cushioning beads are prepared by extrusion-spheronization, followed by freeze-drying.

Claim 17. The tablet as claimed in Claim 16, wherein said microcrystalline cellulose is present in the cushioning beads in an amount of from about 20-100%.

Claim 18. The tablet as claimed in Claim 17, wherein said microcrystalline cellulose is present in

the cushioning beads in an amount of from about 60-95%.

Claim 19. The tablet as claimed in Claim 16, wherein said cushioning beads additionally comprise a disintegrant.

Claim 20. The tablet as claimed in Claim 19, wherein said disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, starch, and pregelatinized starch.

Claim 21. The tablet as claimed in Claim 20, wherein said disintegrant is croscarmellose sodium.

Claim 22. The tablet as claimed in Claim 19, wherein said disintegrant is present in the cushioning beads in an amount of from greater than 0-50%.

Claim 23. The tablet as claimed in Claim 22, wherein said disintegrant is present in the cushioning beads in an amount of from about 5.0-40%.

Claim 24. The tablet as claimed in Claim 19, wherein the ratio of microcrystalline cellulose to disintegrant is about 1:0-0.2:0.8.

Claim 25. The tablet as claimed in Claim 24, wherein the ratio of microcrystalline cellulose to disintegrant is about 0.95:0.05-0.6:0.4.

Claim 26. The tablet as claimed in Claim 19, wherein said cushioning beads additionally comprise a filler.

Claim 27. The tablet as claimed in Claim 26, wherein said filler is a water-soluble filler selected from the group consisting of lactose and sorbitol.

Claim 28. The tablet as claimed in Claim 26, wherein said filler is dibasic calcium phosphate.

Claim 29. The tablet as claimed in Claim 26, wherein said filler is present in the cushioning beads in an amount of from greater than 0-80%.

Claim 30. The tablet as claimed in Claim 29, wherein said filler is present in the cushioning beads in an amount of from greater than 0-50%.

Claim 31. The tablet as claimed in Claim 16, wherein said biologically active ingredient is selected from the group consisting of a pharmaceutical, a pesticide and a herbicide.

Claim 32. The tablet as claimed in Claim 31, wherein said pharmaceutical is selected from the group consisting of potassium chloride, a lithium salt, a nonsteroidal anti-inflammatory drug, a calcium salt, sodium fluoride, pridinol or a salt thereof, dimethindine or a salt thereof, a methyl-xanthine, o-β-hydroxymethyl-rutoside, butamirate or a salt thereof, codeine or a derivative thereof, noscapine, acetaminophen, a vitamin, a β-blocker, pyrisuccideanol, ticlopidine, dipyridamole, diazepam, erythromycin or a salt thereof, and doxycycline or a salt thereof.

Claim 33. The tablet as claimed in Claim 31, wherein said pesticide is selected from the group consisting of clomazone, sulfentrazone and clomazone/trifluralin.

Claim 34. The tablet as claimed in Claim 31, wherein said herbicide is selected from the group consisting of zeta cypermephrin, cadusafos and bifenthrin.

Claim 35. The tablet as claimed in Claim 16, said biologically active ingredient-loaded beads are coated with a coating material for controlling or sustaining the release properties of the biologically active ingredient, for taste masking, or for imparting resistance to gastric fluid, or said biologically active ingredient-loaded beads contain said material in the matrix thereof.

Claim 36. The tablet as claimed in Claim 35, said coating material for controlling or sustaining the release properties of the biologically active ingredient and for taste masking is selected from the group consisting of methylcellulose, hydroxypropyl cellulose, ethylcellulose or a latex derivative thereof, and a methylacrylate ester copolymer.

Claim 37. The tablet as claimed in Claim 35, said coating material for imparting resistance to gastric fluid is selected from the group consisting of shellac, cellulose acetate phthalate, cellulose acetate trimelliate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose acetate succinate, and a methacrylic acid copolymer.

Claim 38. The tablet of Claim 19, wherein said tablet additionally comprises:

(iii) a viscosity enhancer.

Claim 39. The tablet of Claim 38, wherein said viscosity enhancer is in the form of individual viscosity enhancer beads.

Claim 40. The tablet of Claim 38, wherein said viscosity enhancer is present in the biologically active ingredient-loaded beads.

Claim 41. The tablet of Claim 38, wherein said viscosity enhancer is selected from the group consisting of a carbomer, xanthan gum, guar gum, alginate, dextran, pectin, pregelatinized starch, polysaccharide and a cellulose derivative.

Claim 42. The tablet of Claim 41, wherein said cellulose derivative is selected from the group consisting of sodium or calcium carboxymethlycellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose.

Claim 43. The tablet of Claim 41, wherein said viscosity enhancer is a carbomer.

Claim 44. The tablet of Claim 39, wherein said viscosity enhancer beads are produced by extrusion-spheronization using a hydroalcoholic solution.

Claim 45. The tablet of Claim 16, wherein said cushioning beads and biologically active ingredient-loaded beads each have an average diameter of about 0.2-2.0 mm.

Claim 46. The tablet of Claim 45, wherein said cushioning beads and biologically active ingredient-loaded beads each have an average diameter of about 0.5-1.5 mm.

Claim 47. The tablet of Claim 39, wherein said cushioning beads and biologically active ingredient-loaded beads and viscosity enhancer beads each have an average diameter of about 0.2-2.0 mm.

Claim 48. The tablet of Claim 47, wherein said cushioning beads and biologically active ingredient-loaded beads and viscosity enhancer beads each have an average diameter of about 0.5-1.5 mm.

Claim 49. The tablet of Claim 16, wherein the weight ratio of cushioning beads to biologically active ingredient-loaded beads is about 20:80-90:10.

Claim 50. The tablet of Claim 49, wherein the weight ratio of cushioning beads to biologically active ingredient-loaded beads is about 50:50-75:25.

Claim 51. The tablet of Claim 38, wherein the viscosity enhancer is present in an amount to achieve an apparent viscosity, at 20°C, of 30-3000 mPa.s.

Claim 52. The tablet of Claim 51, wherein the viscosity enhancer is present in an amount to achieve an apparent viscosity, at 20°C, of 500-1000 mPa.s.

Claim 53. An *in situ* suspension formed by dispersing the tablet of Claim 38 in an aqueous solution.

Figure 1A

Partially solvated carbomer molecule

Figure 1B

A neutralized, fully solvated carbomer molecule
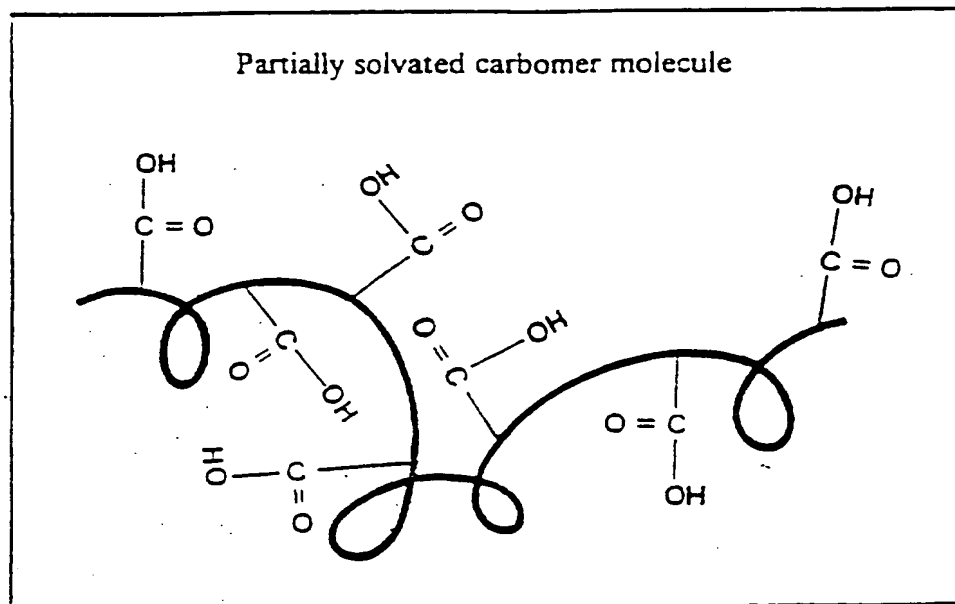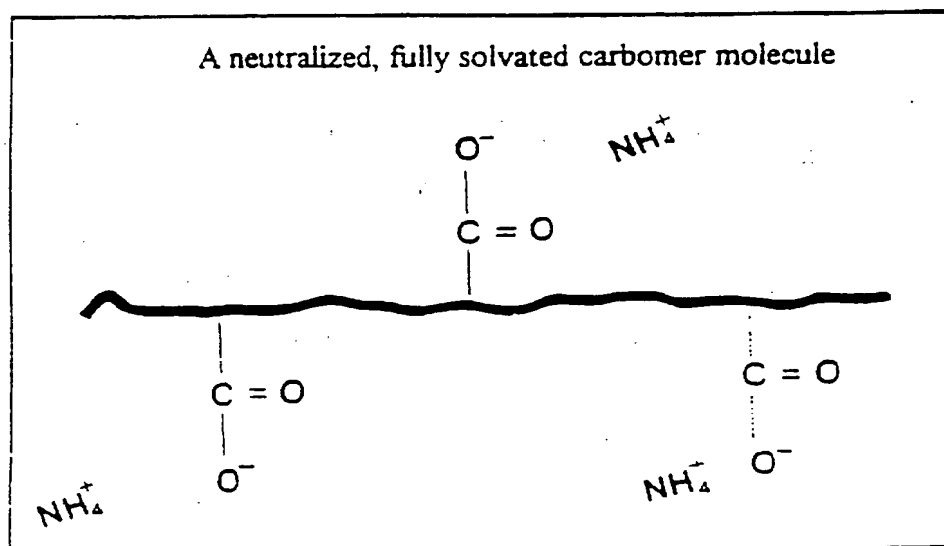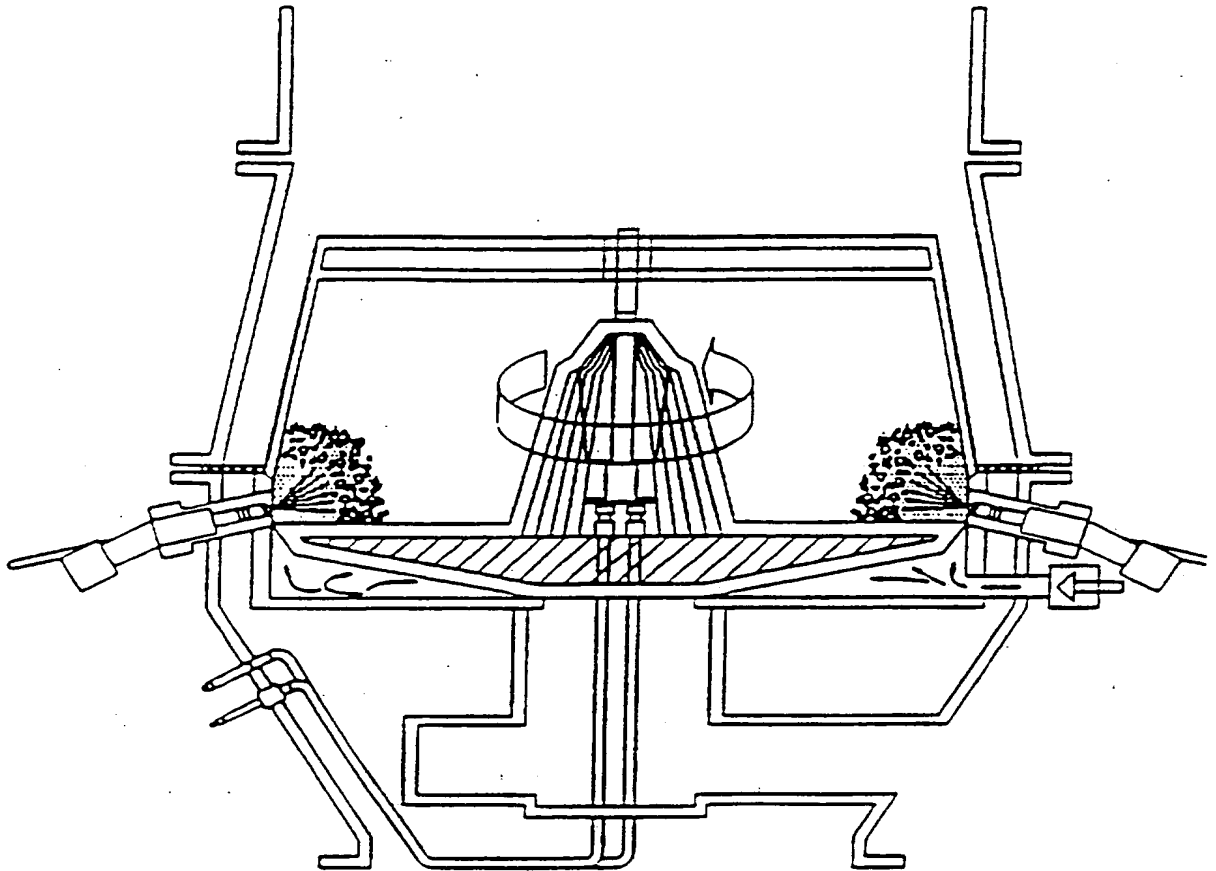
Figure 2

3/55

Figure 3A

Type 1

ln(1/1-D)

P

Figure 3B

Type 2

ln(1/1-D)

P
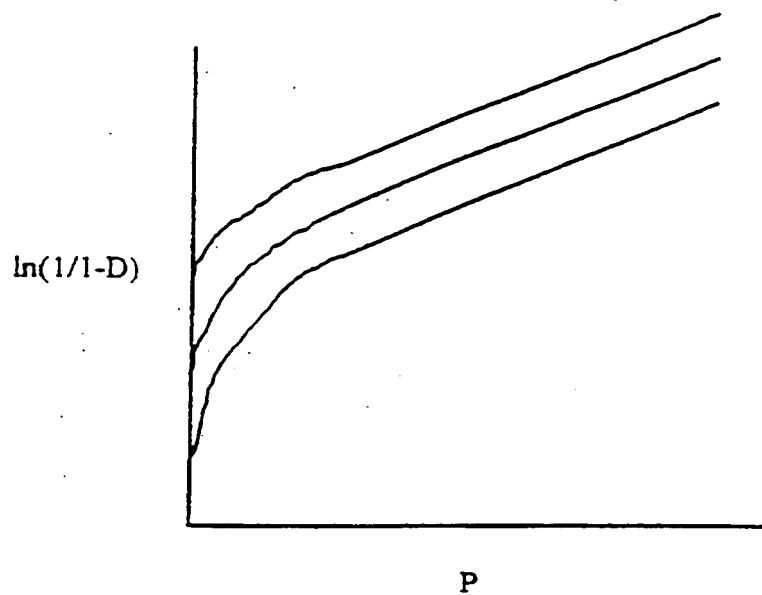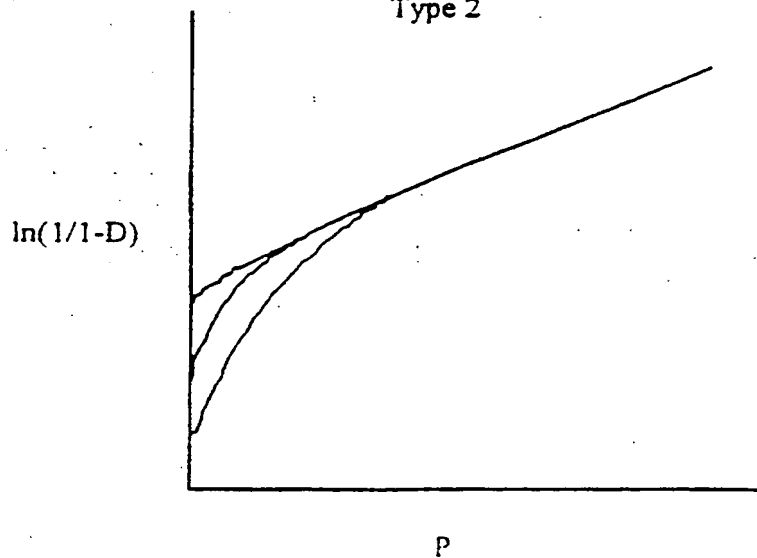
4/55

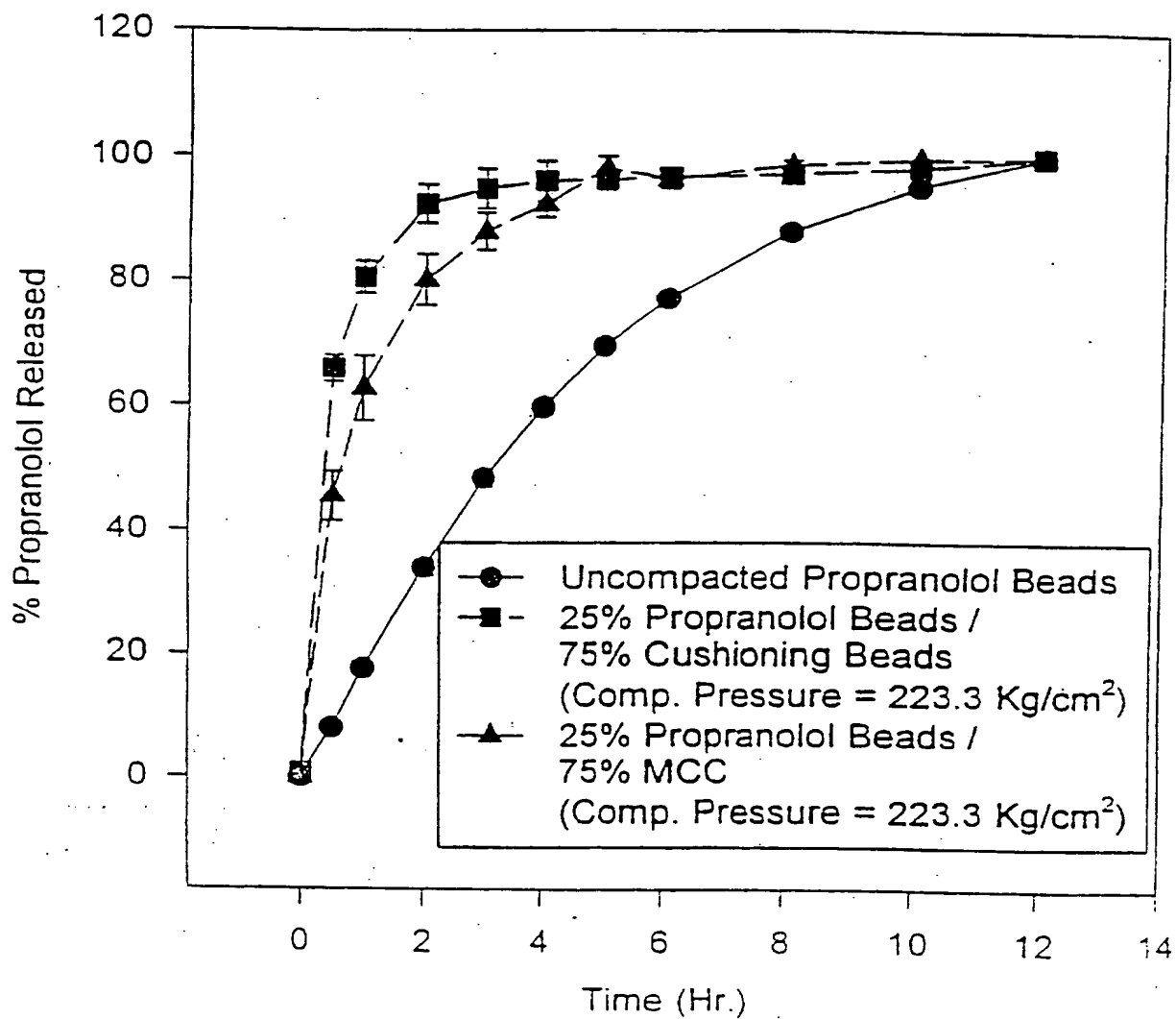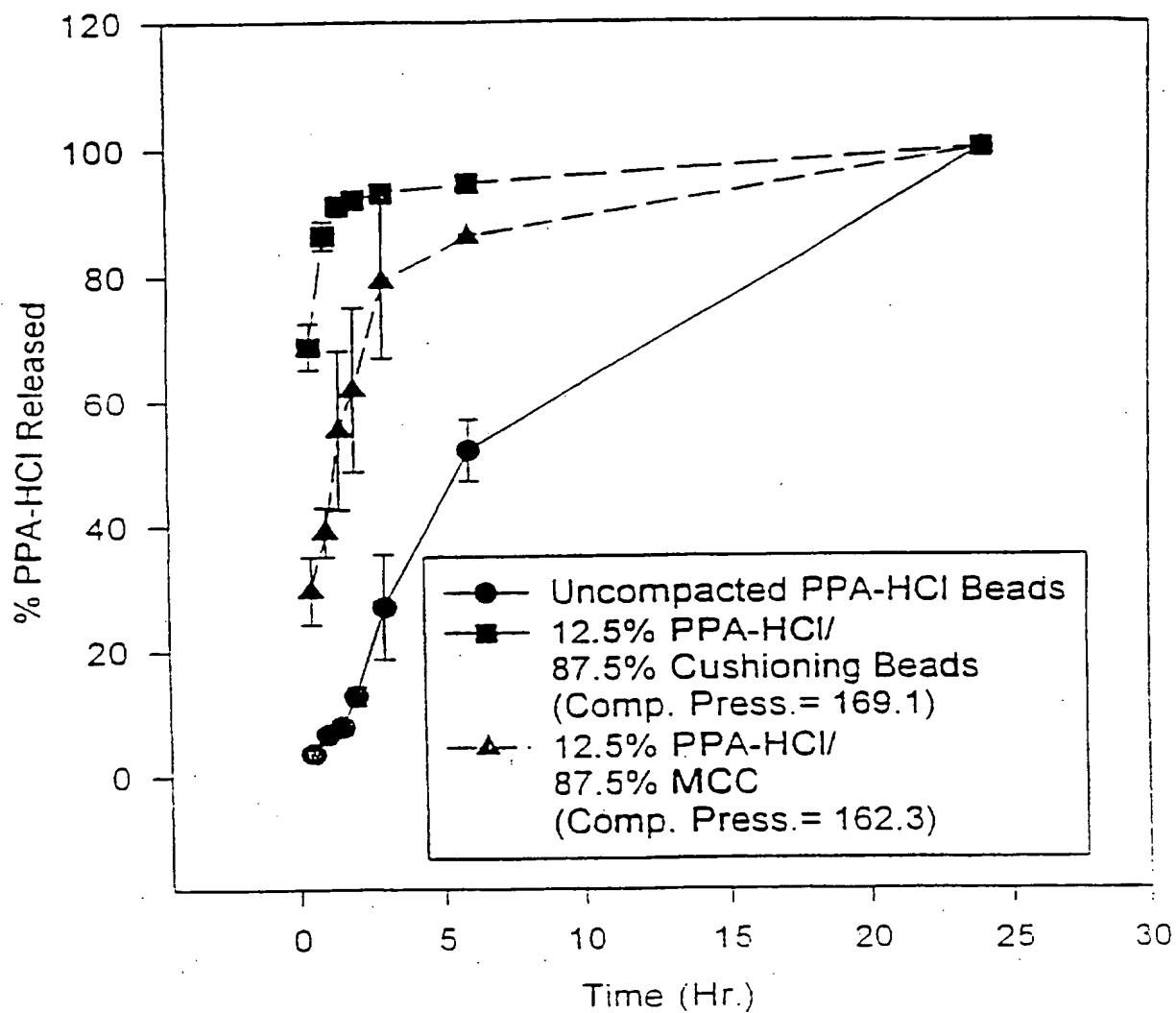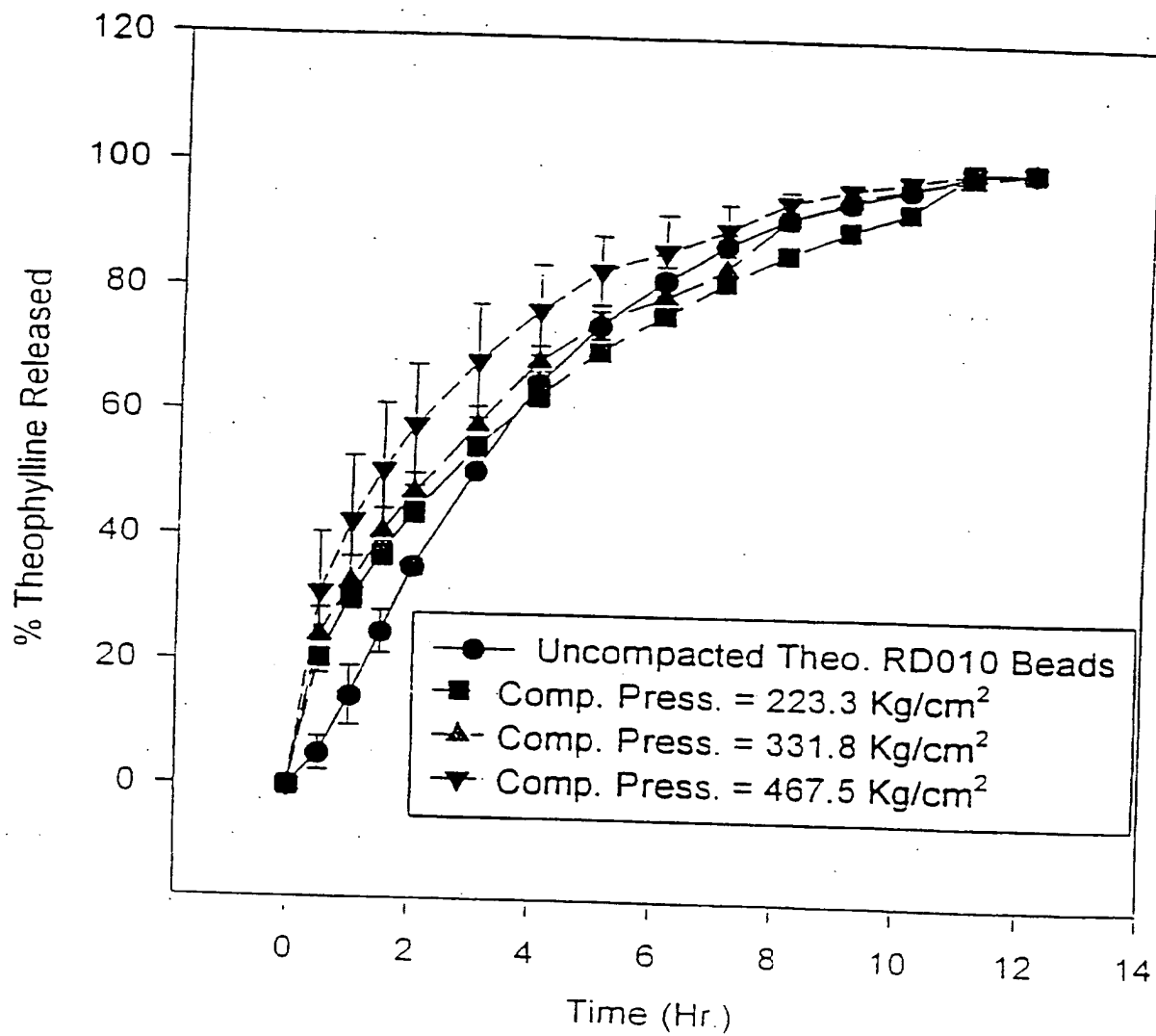Figure 4

5/55
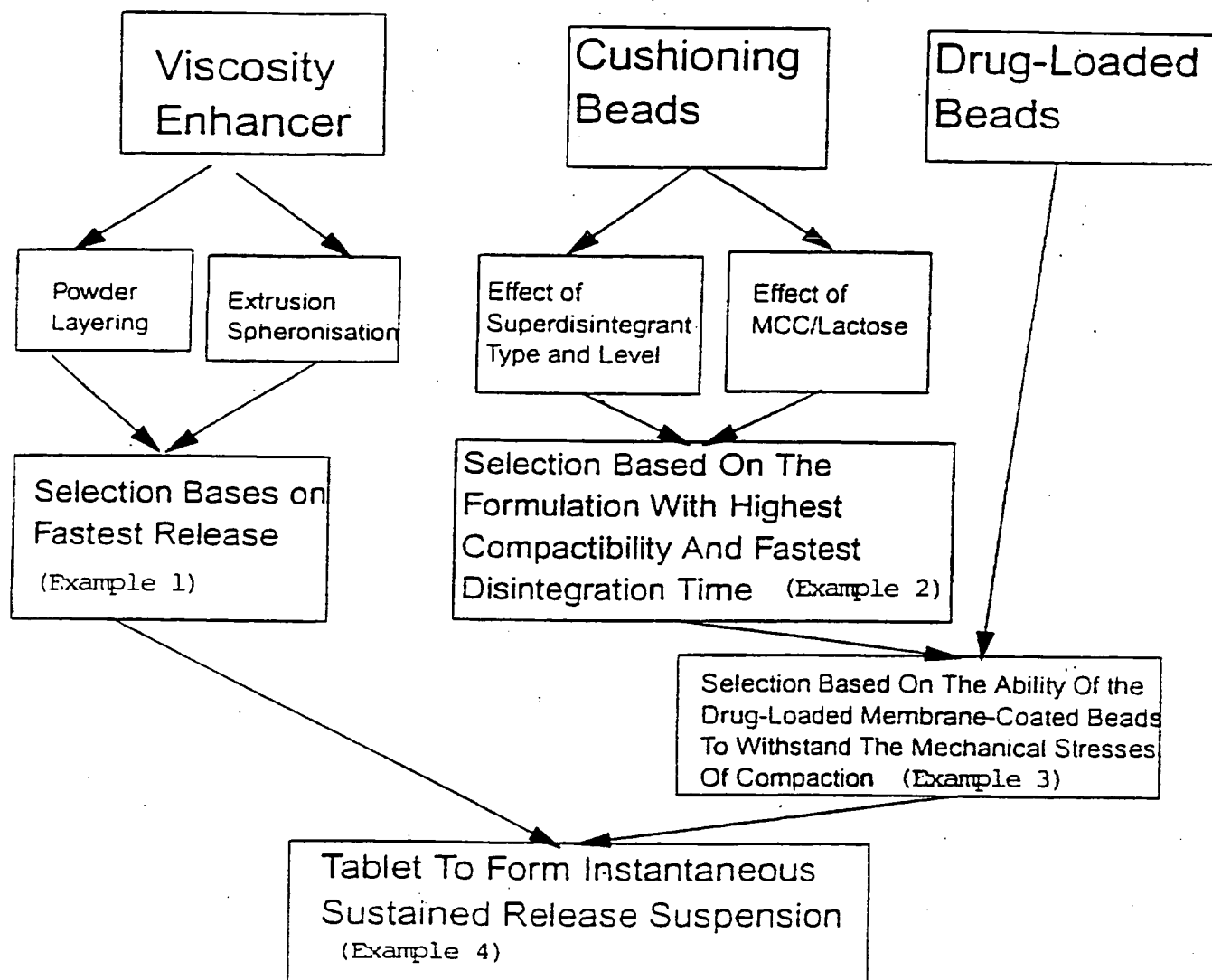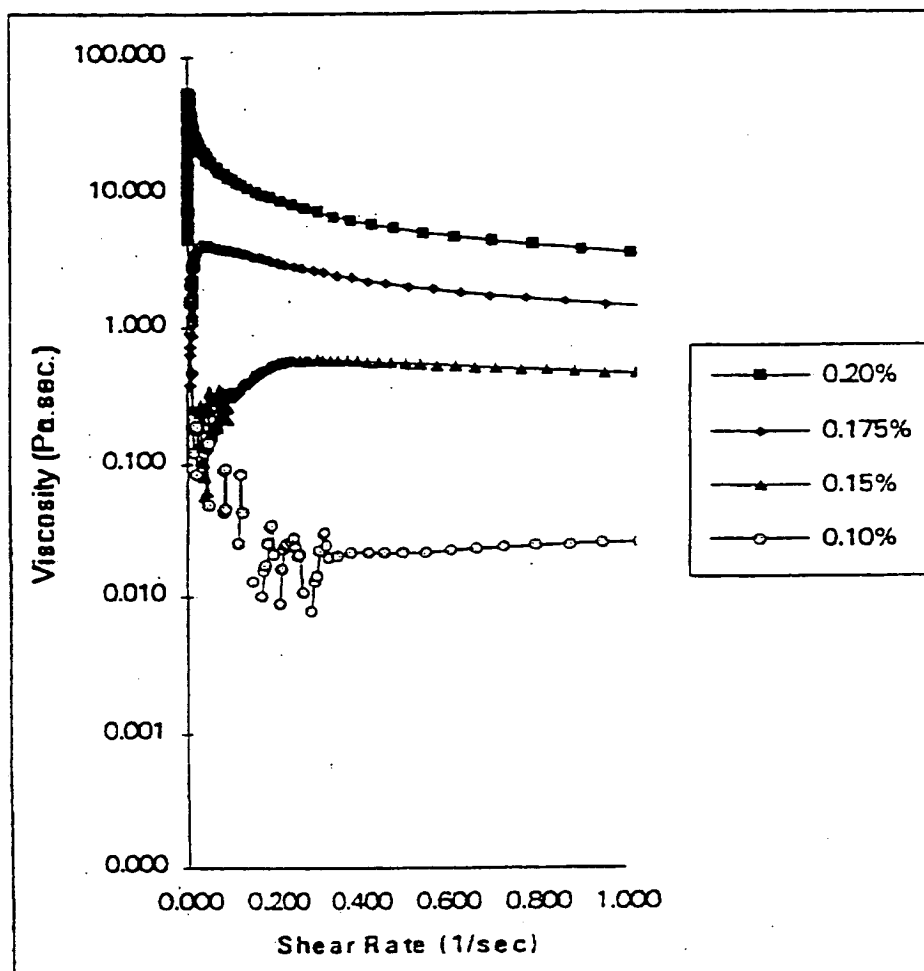
Figure 5

Figure 6

7/55

Figure 7

8/55
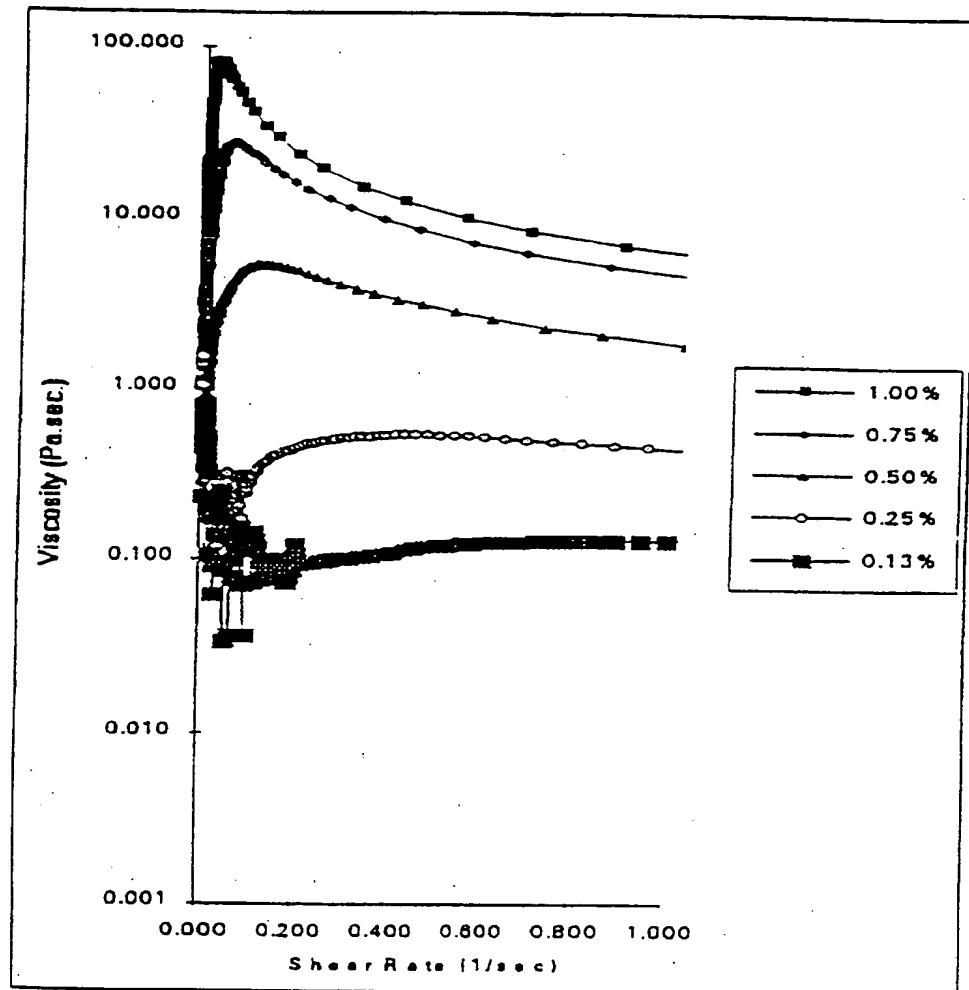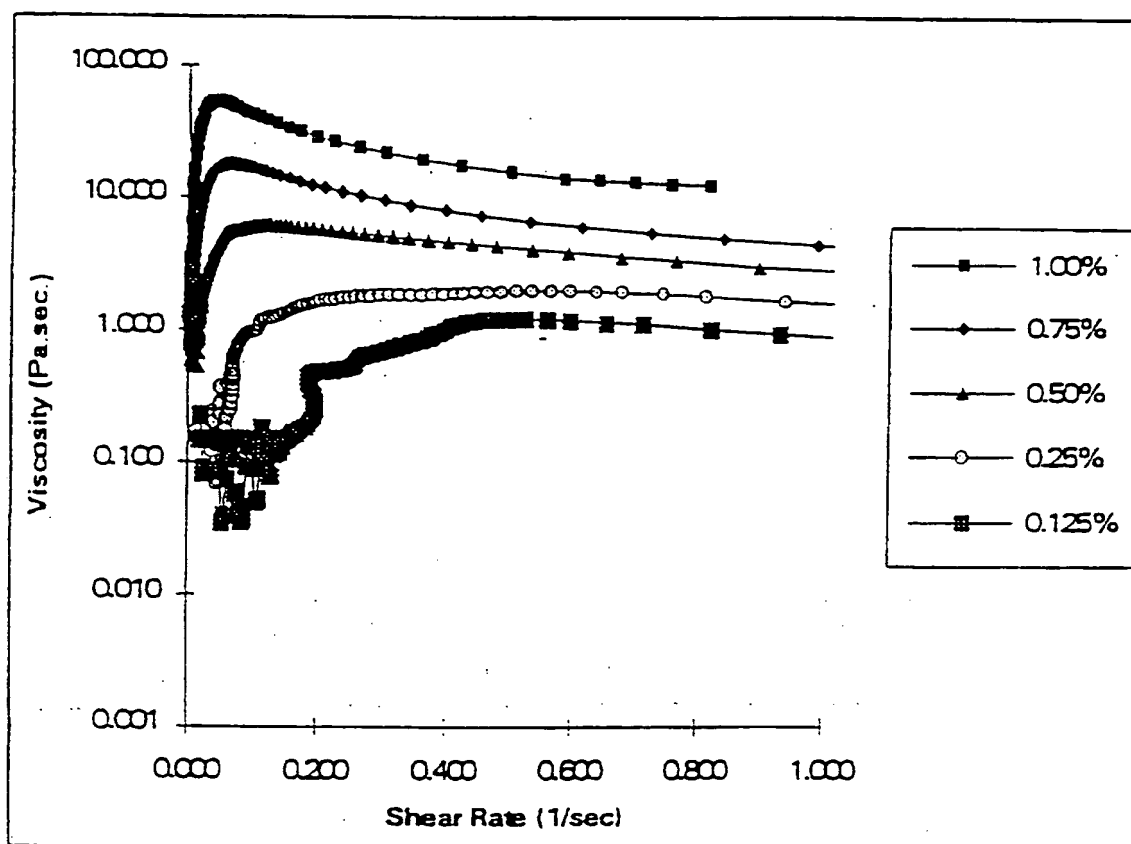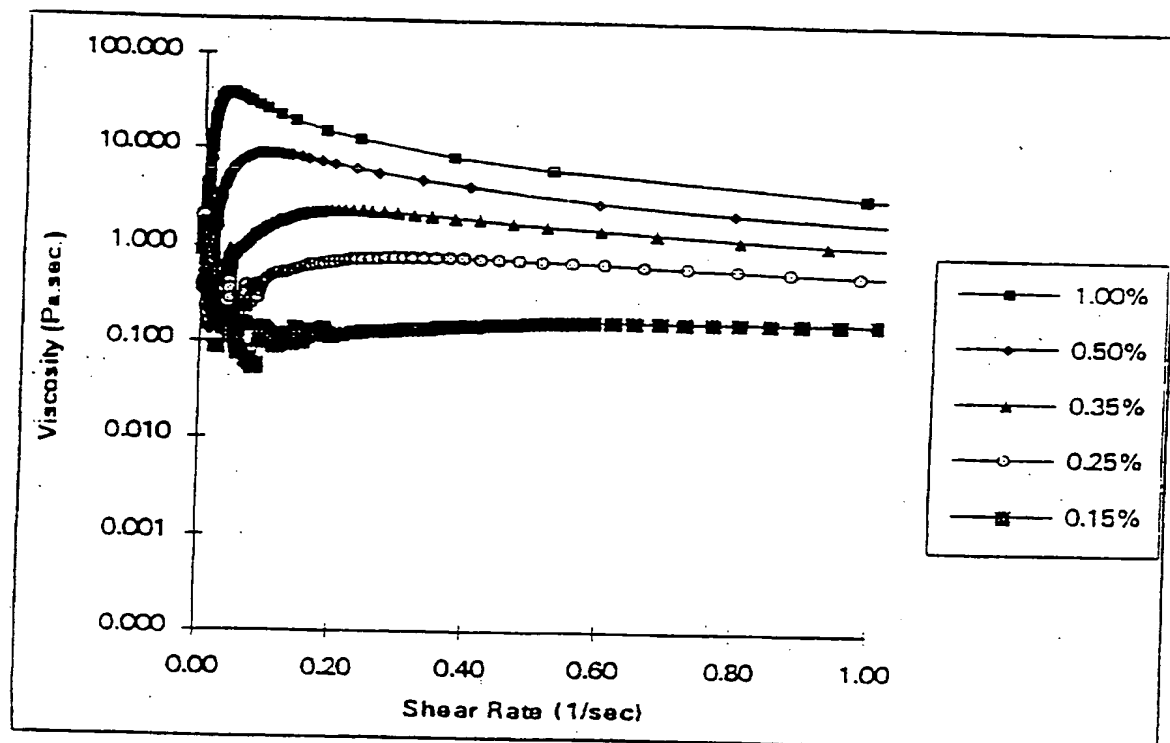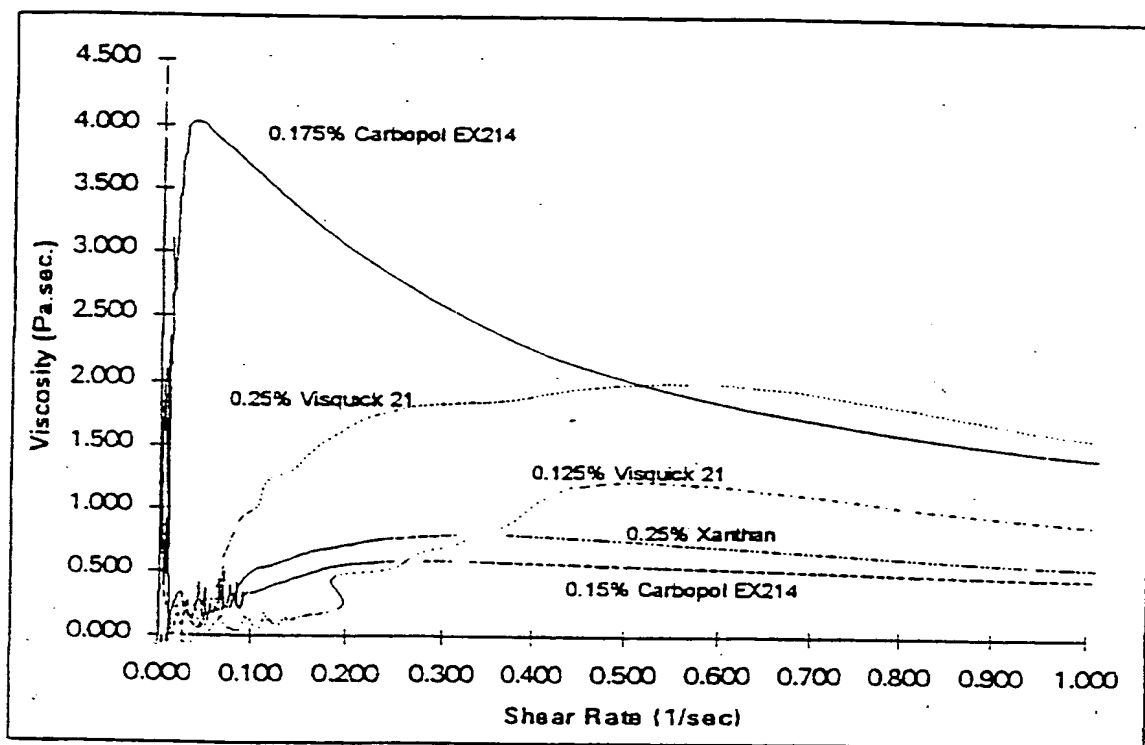
Figure 8
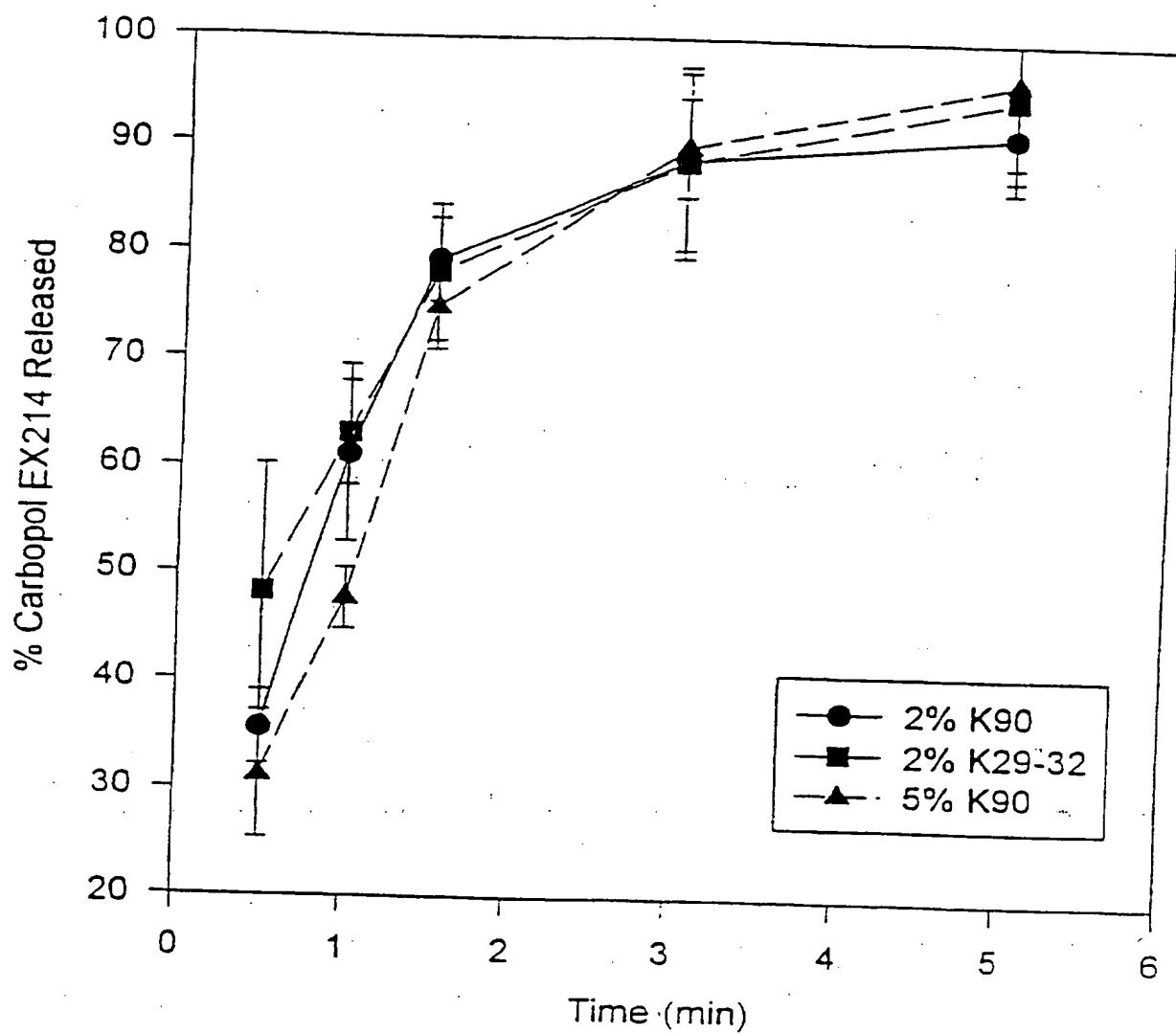
Figure 9

Figure 10

11/55

Figure 11
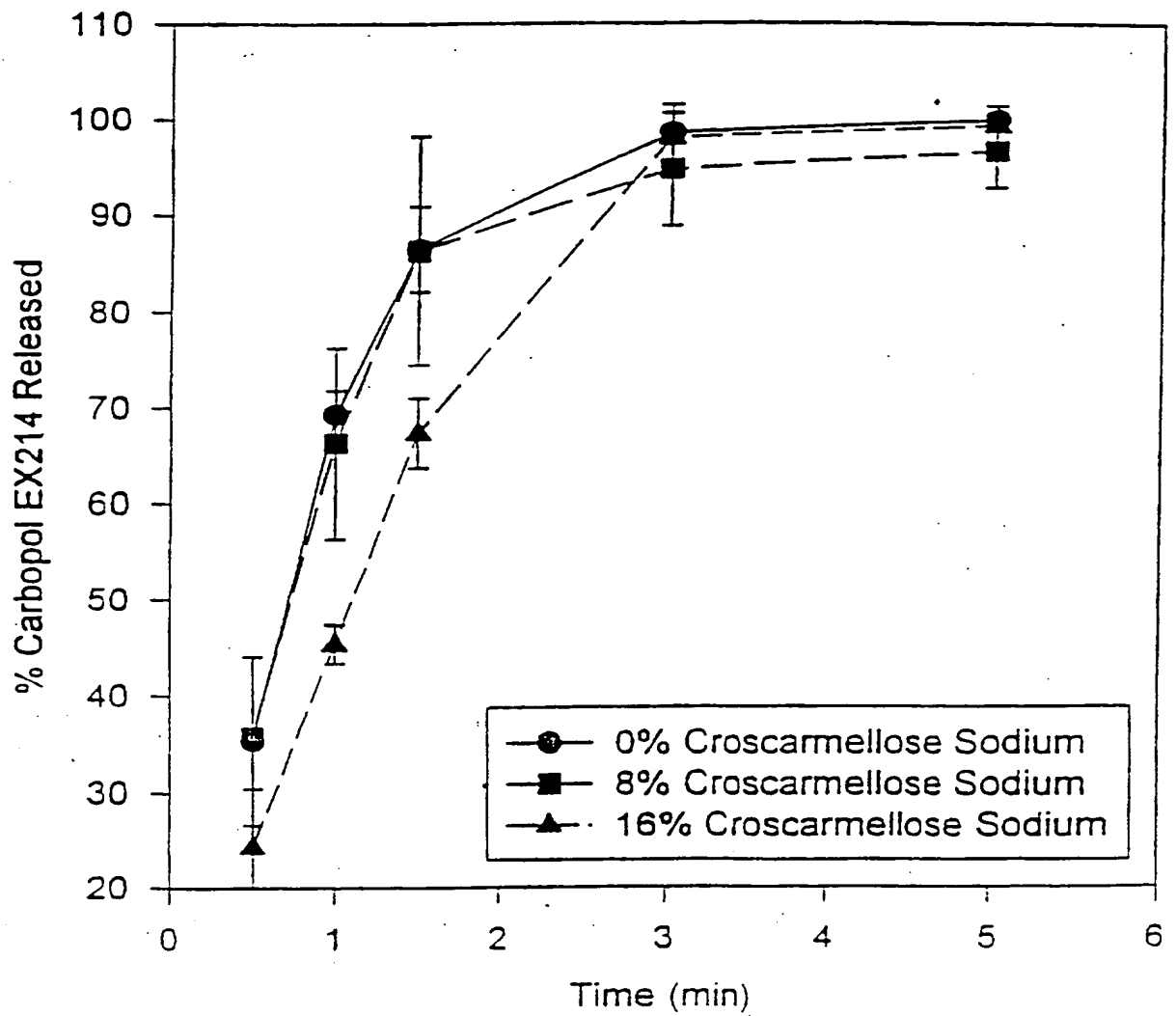
12/55

Figure 12
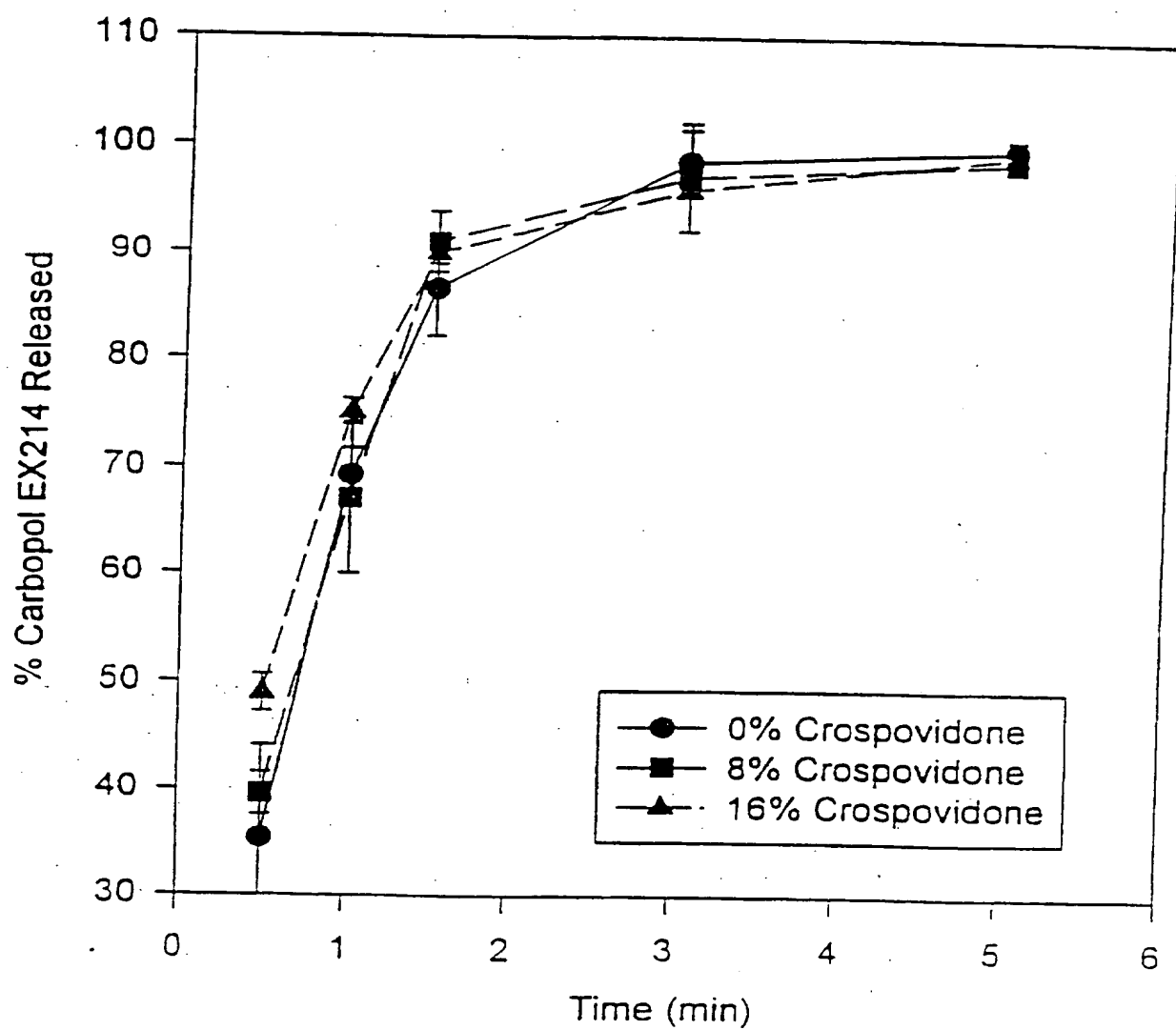
13/55

Figure 13
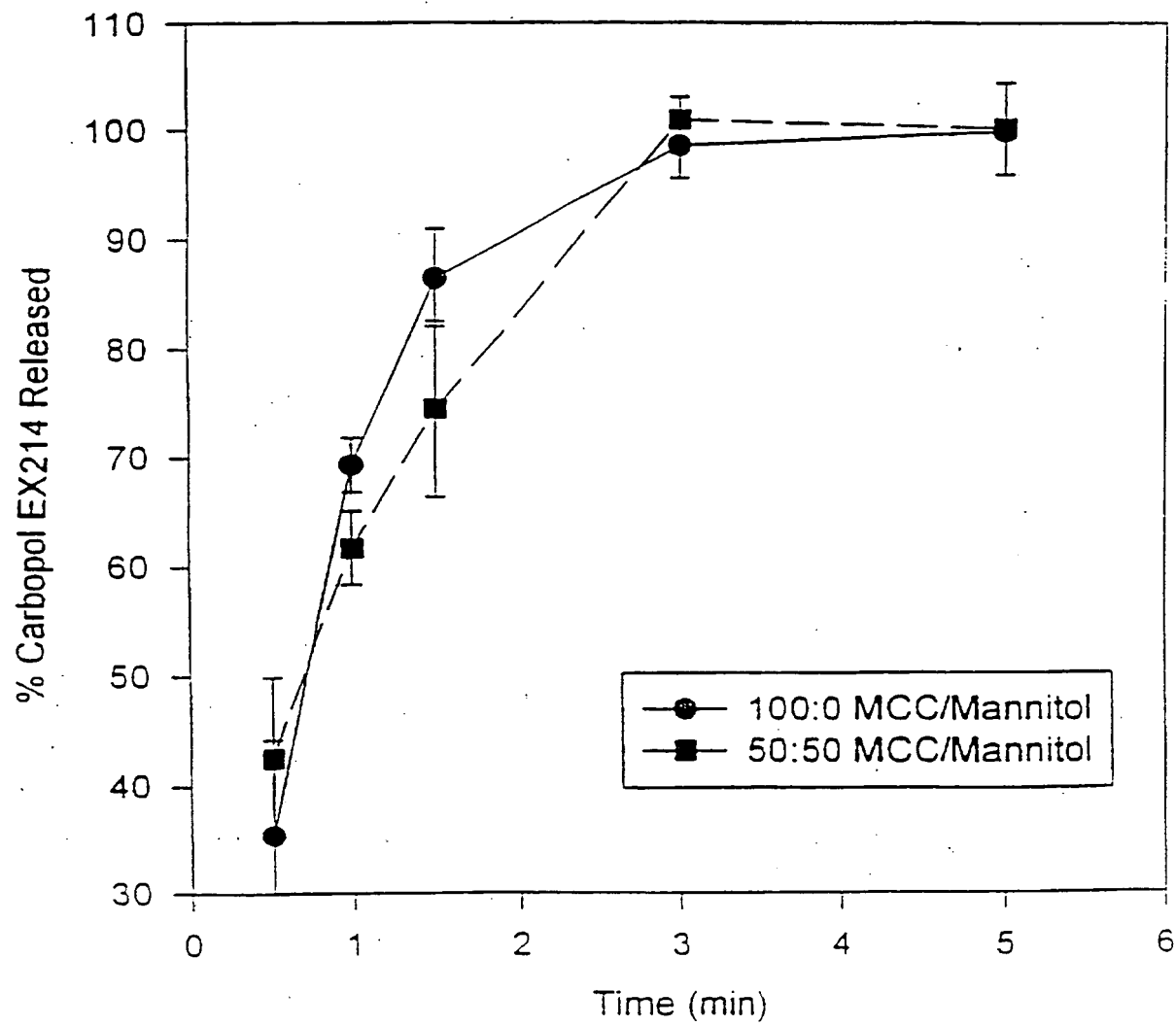
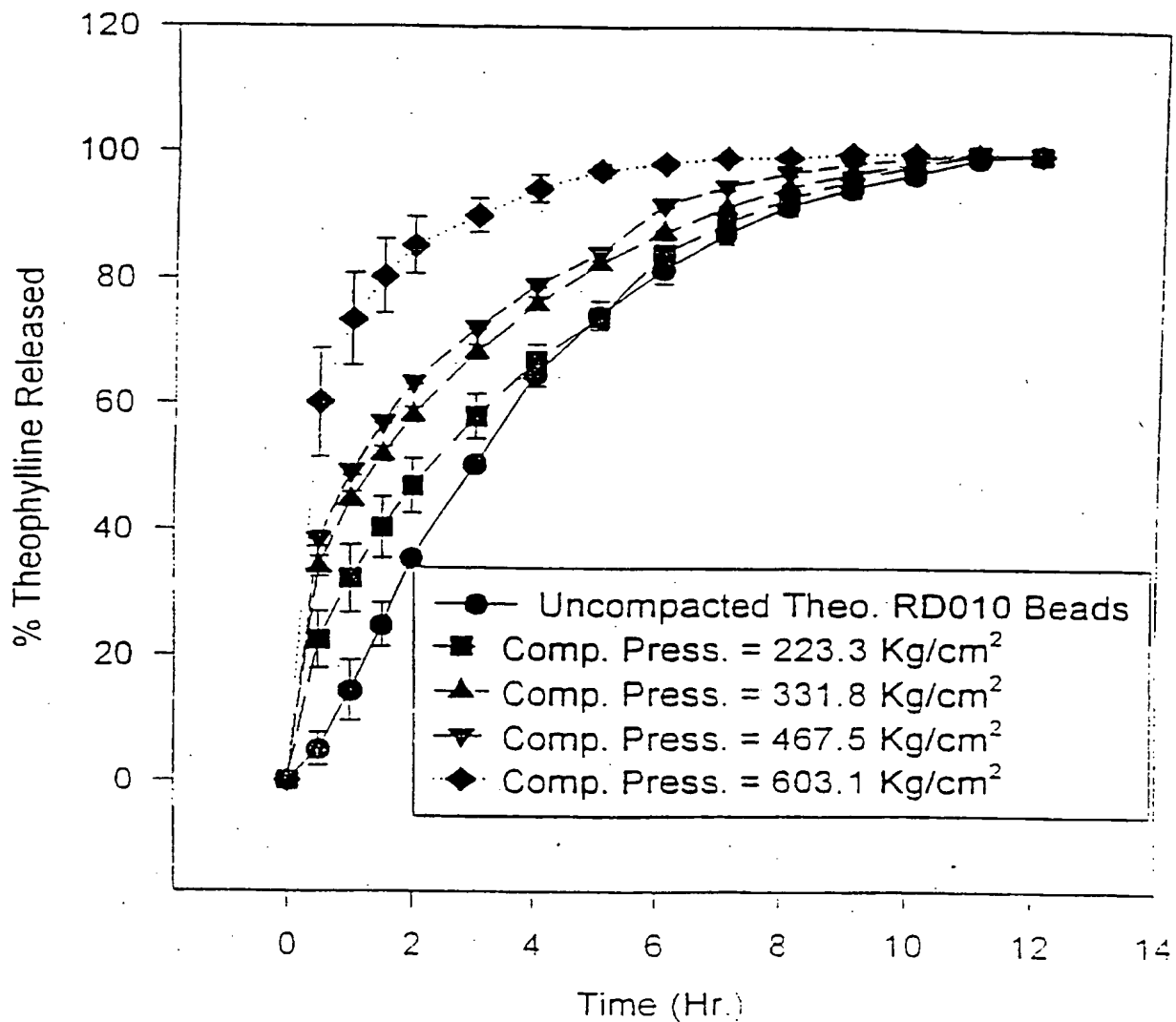14/55

Figure 14
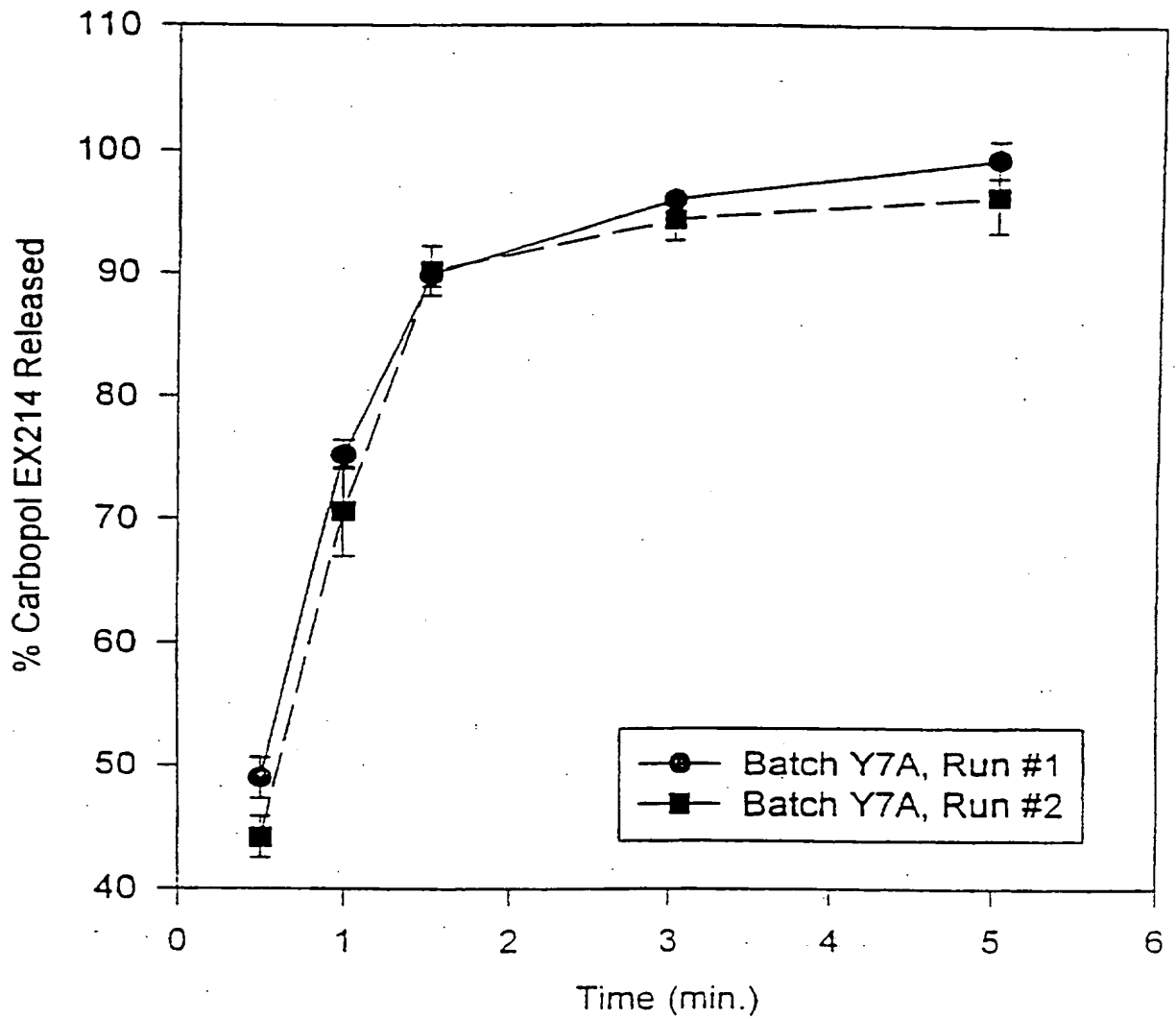
15/55

Figure 15
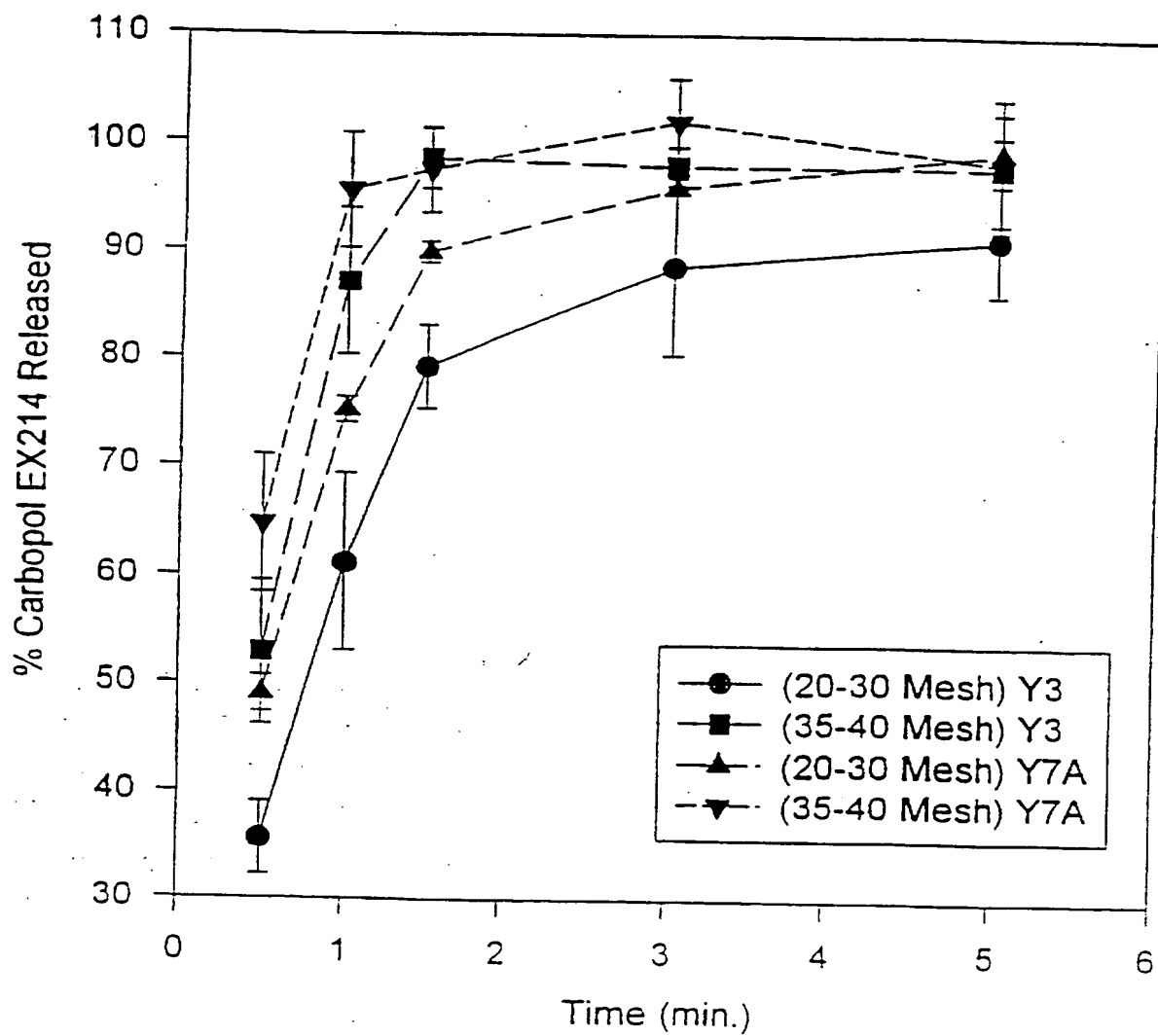
16/55

Figure 16

17/55

Figure 17

Figure 18

12155
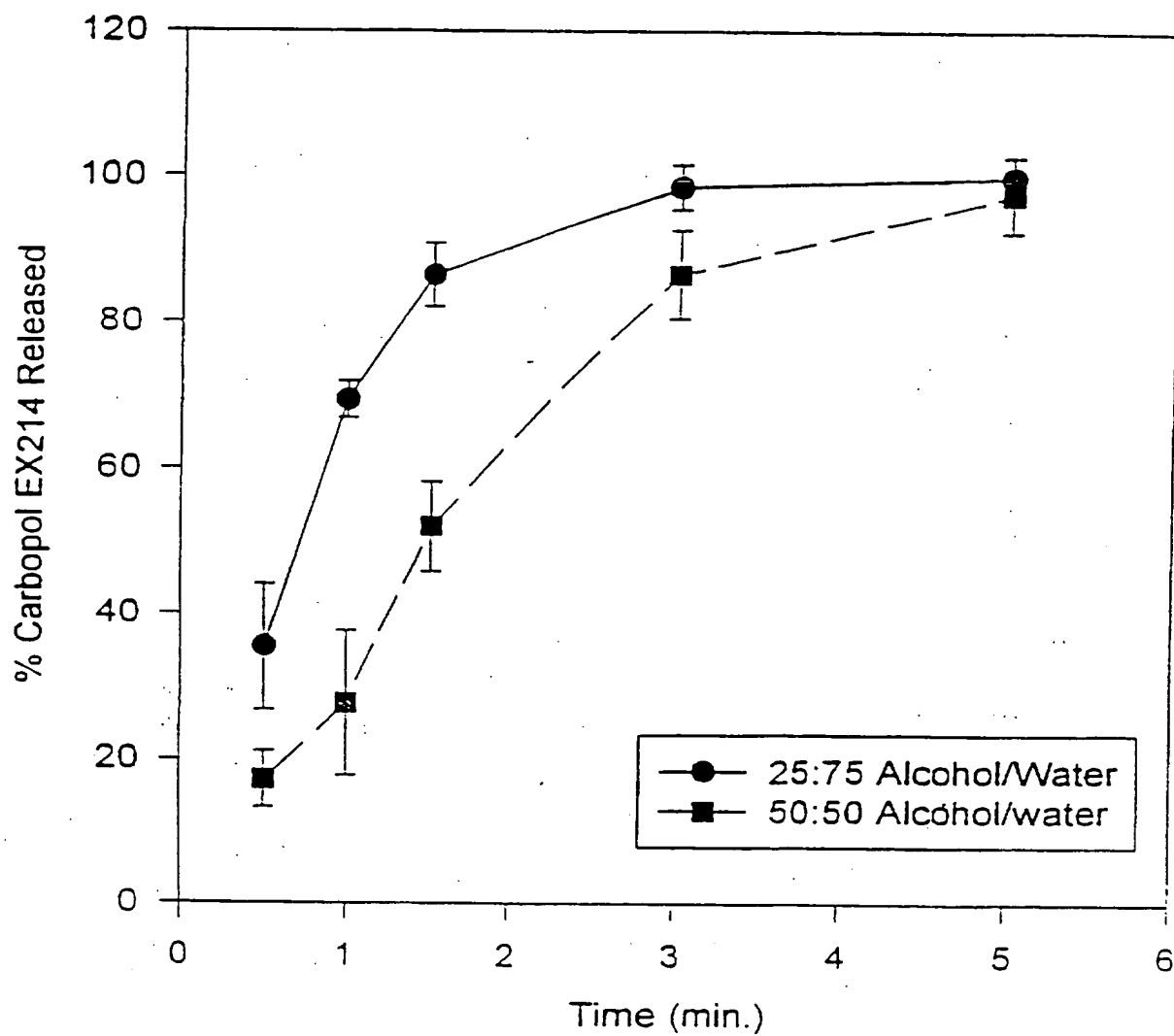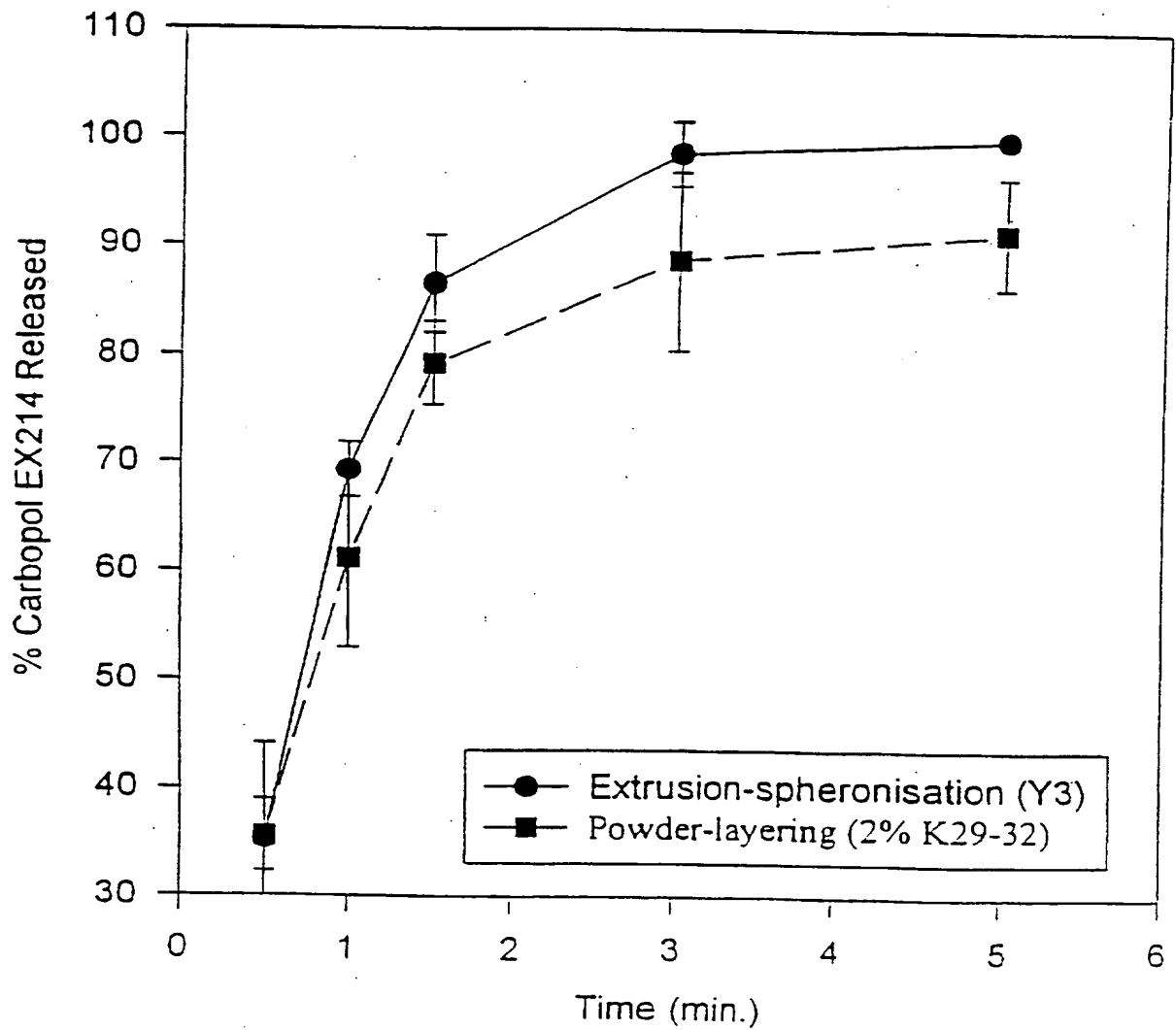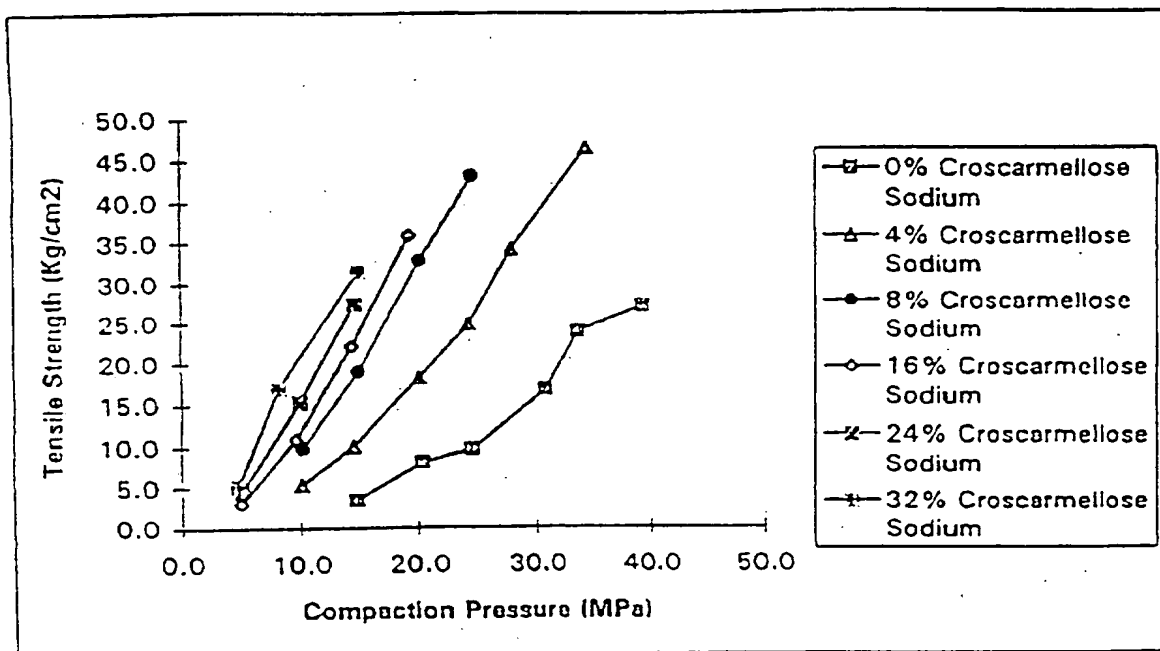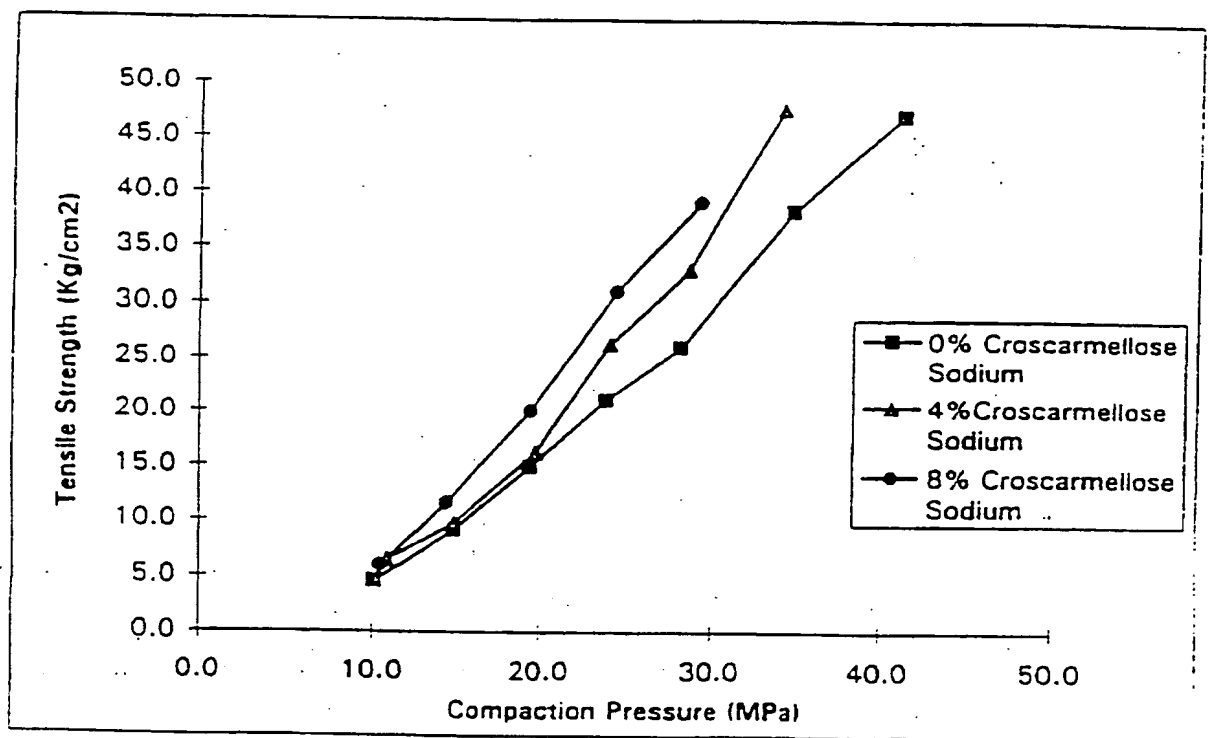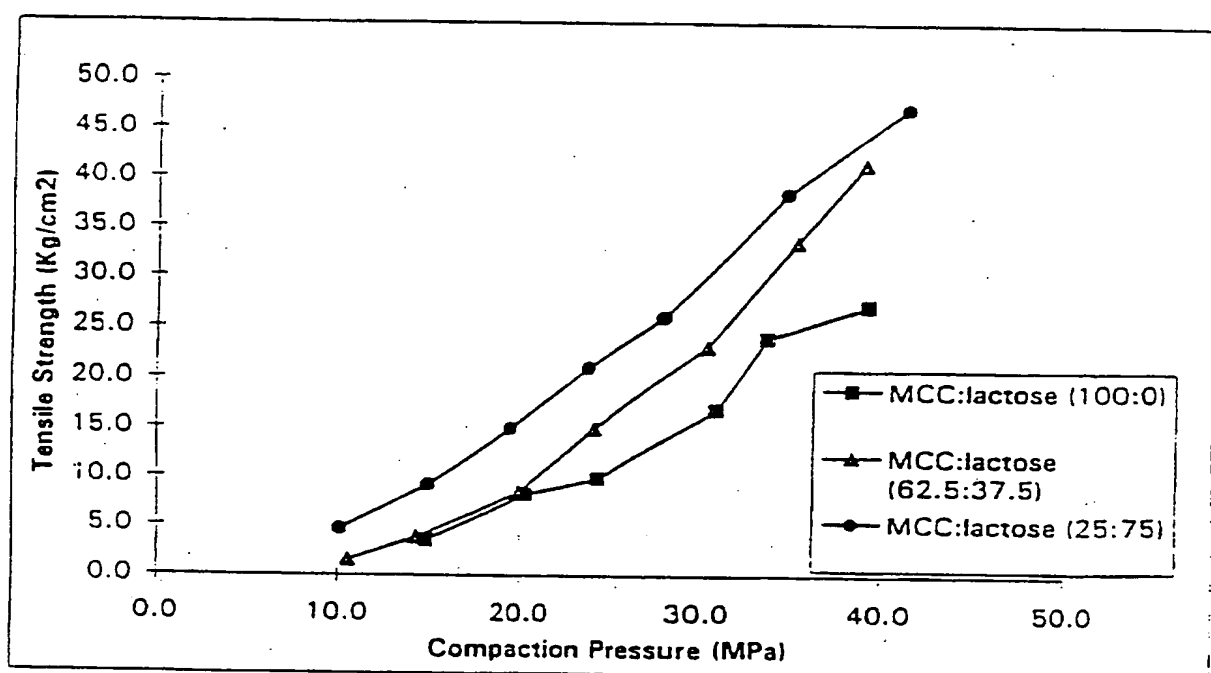
Figure 19

Figure 20

21/55
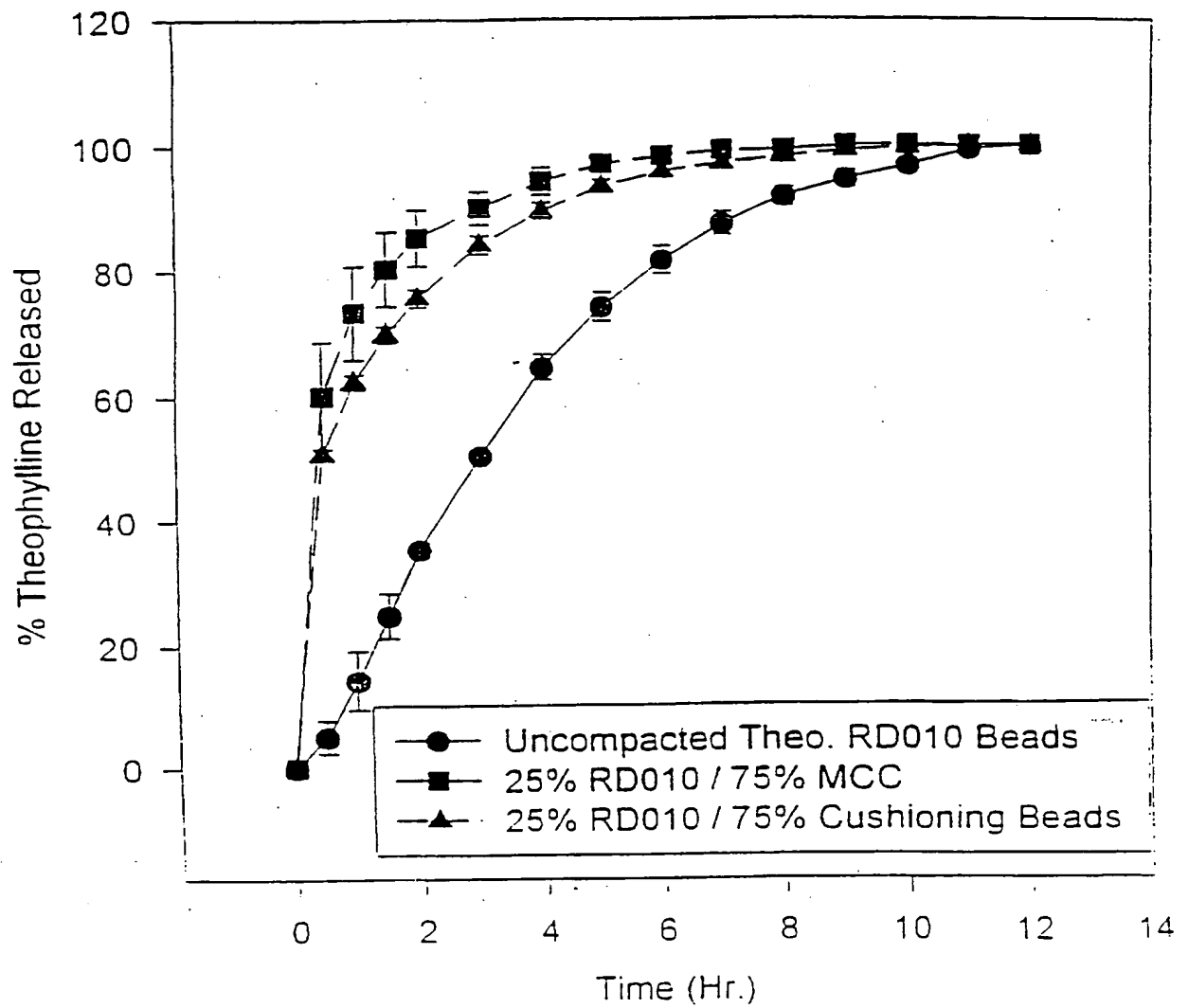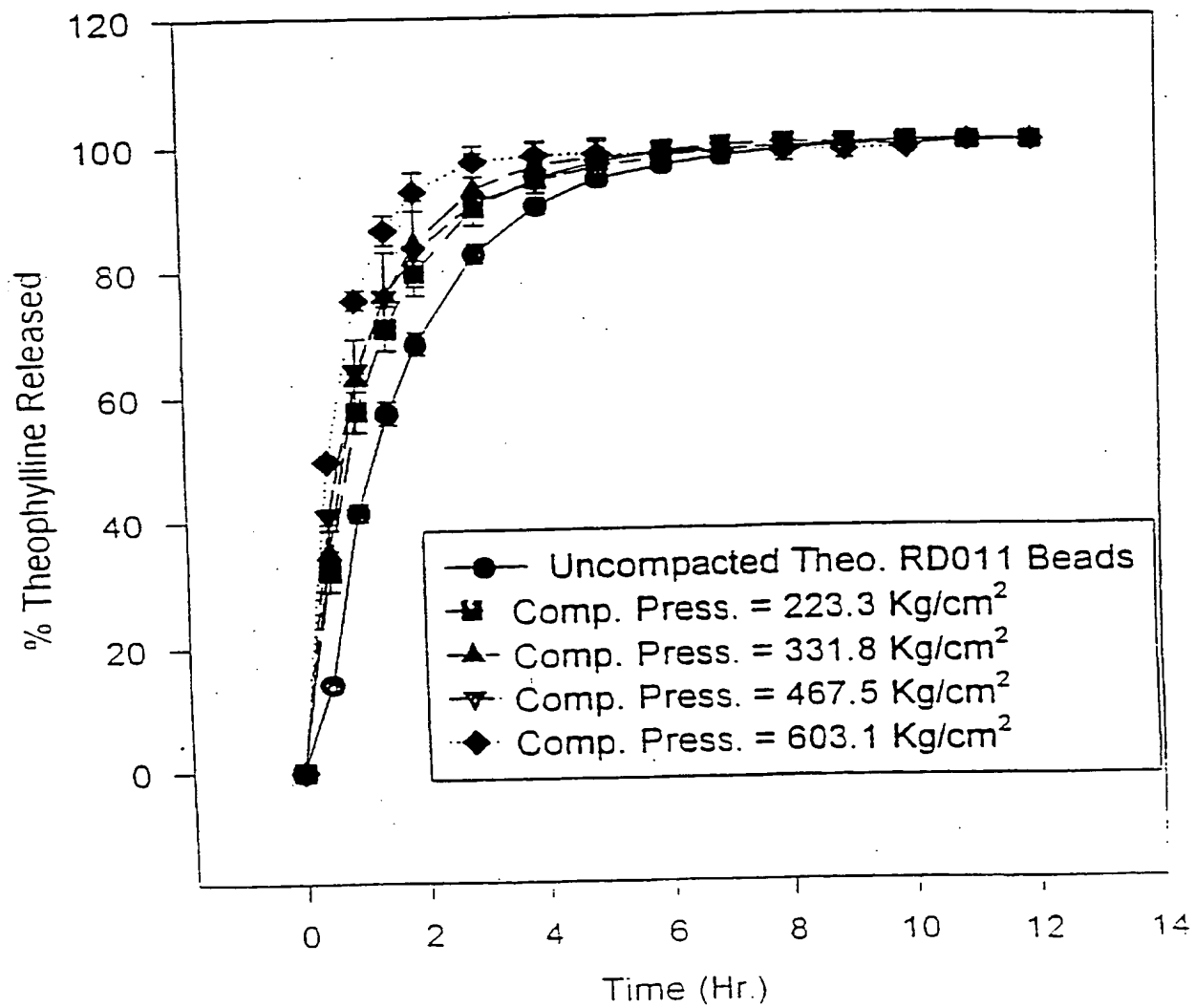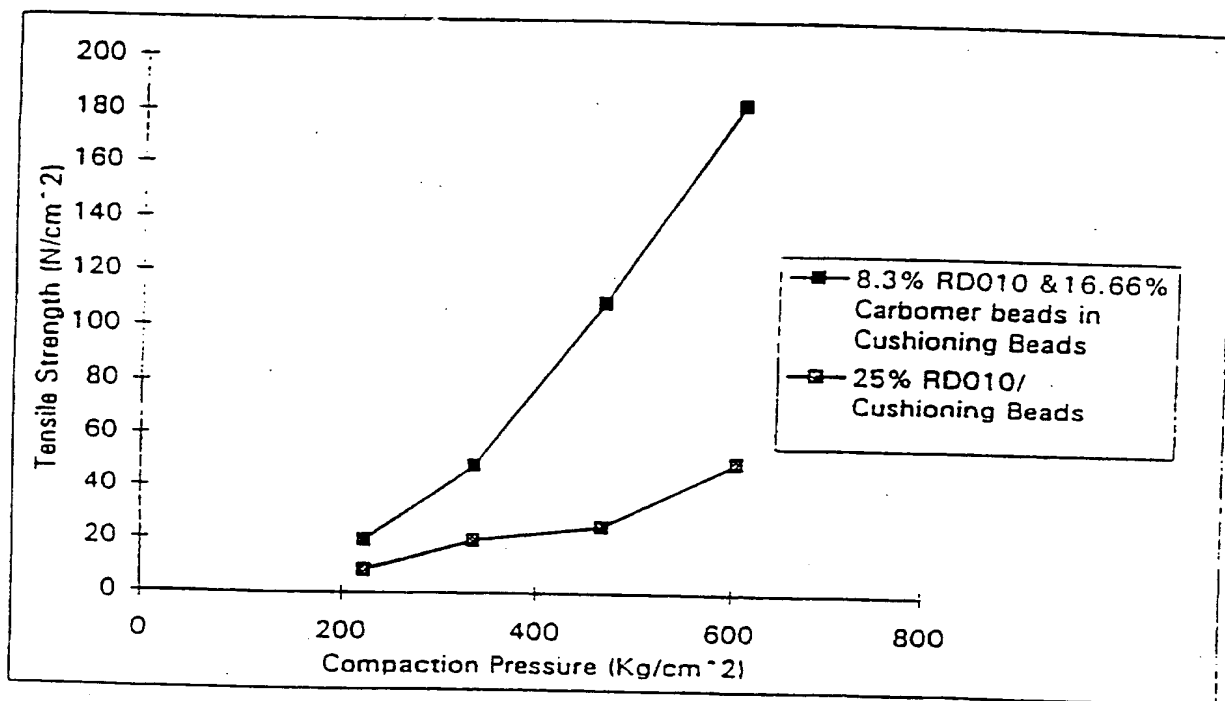
Figure 21
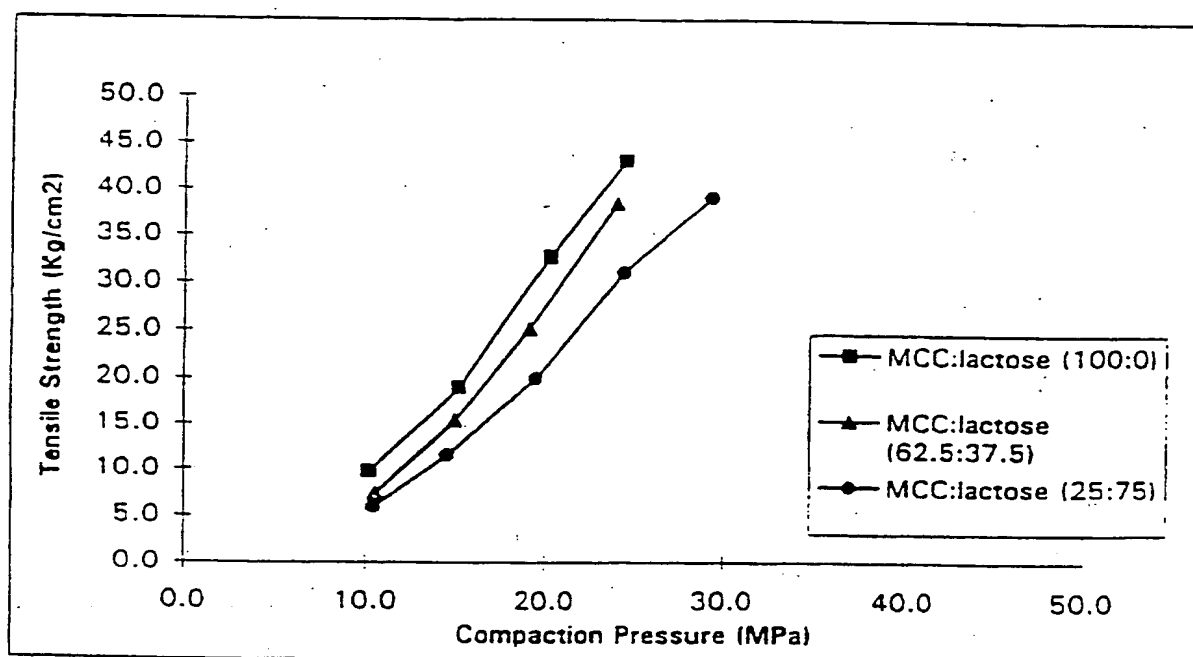
22/55

Figure 22

23/55

Figure 23

24/55
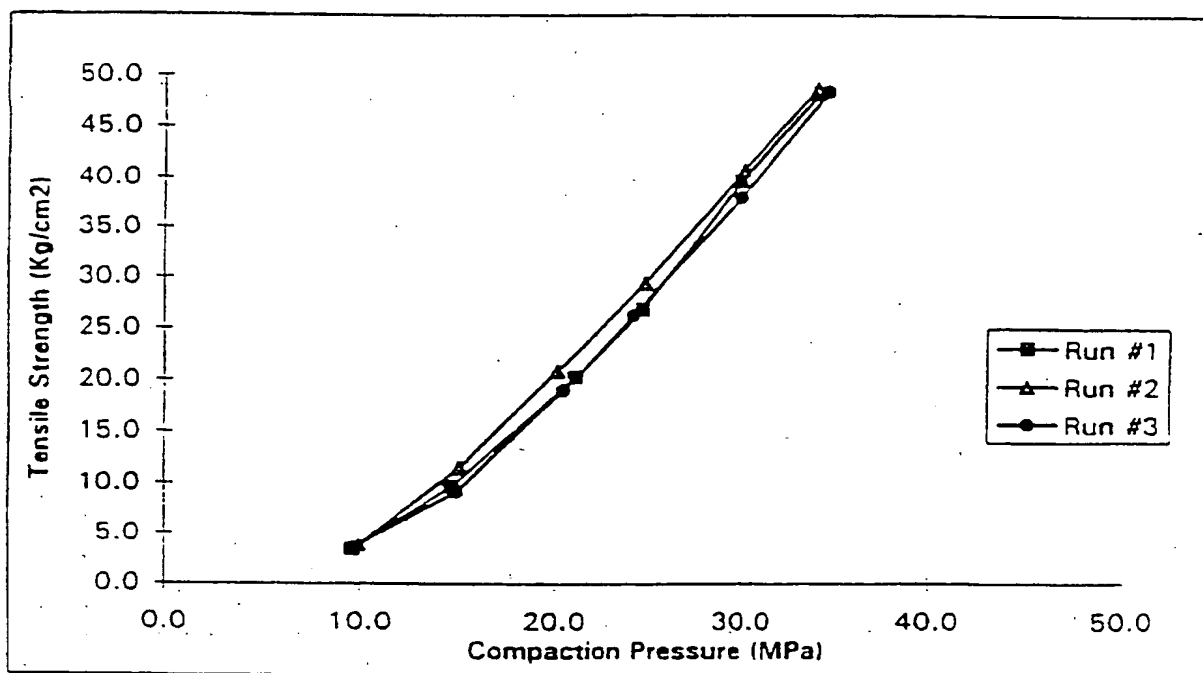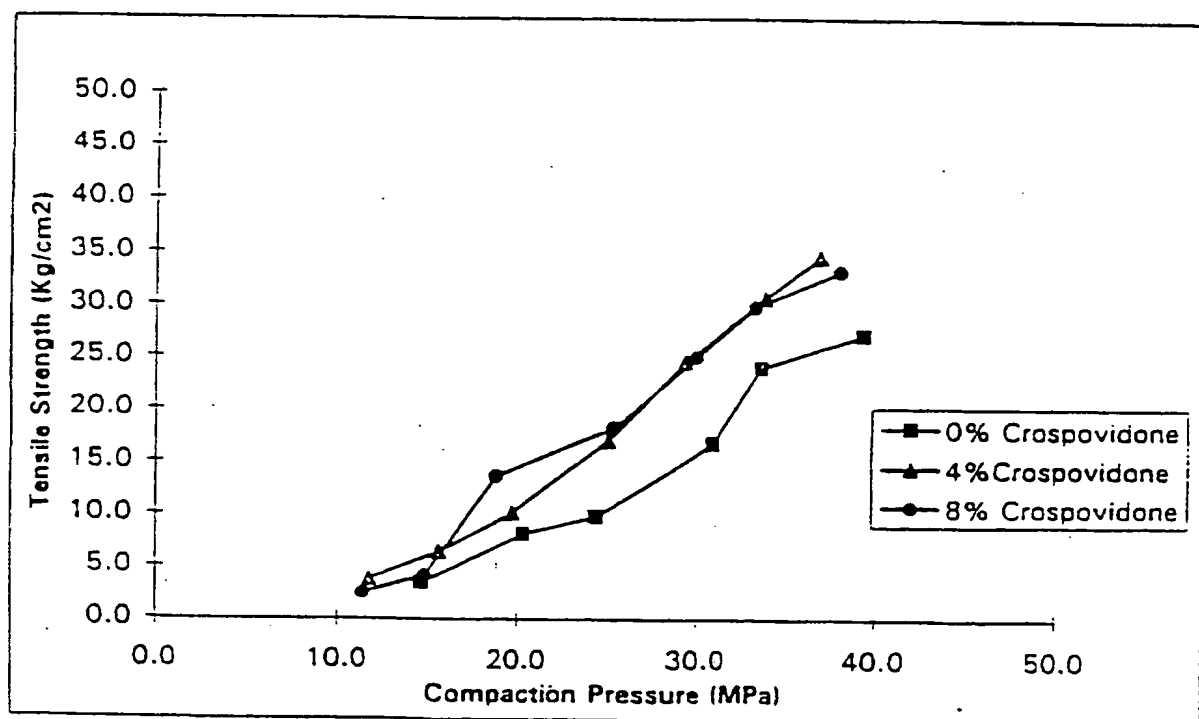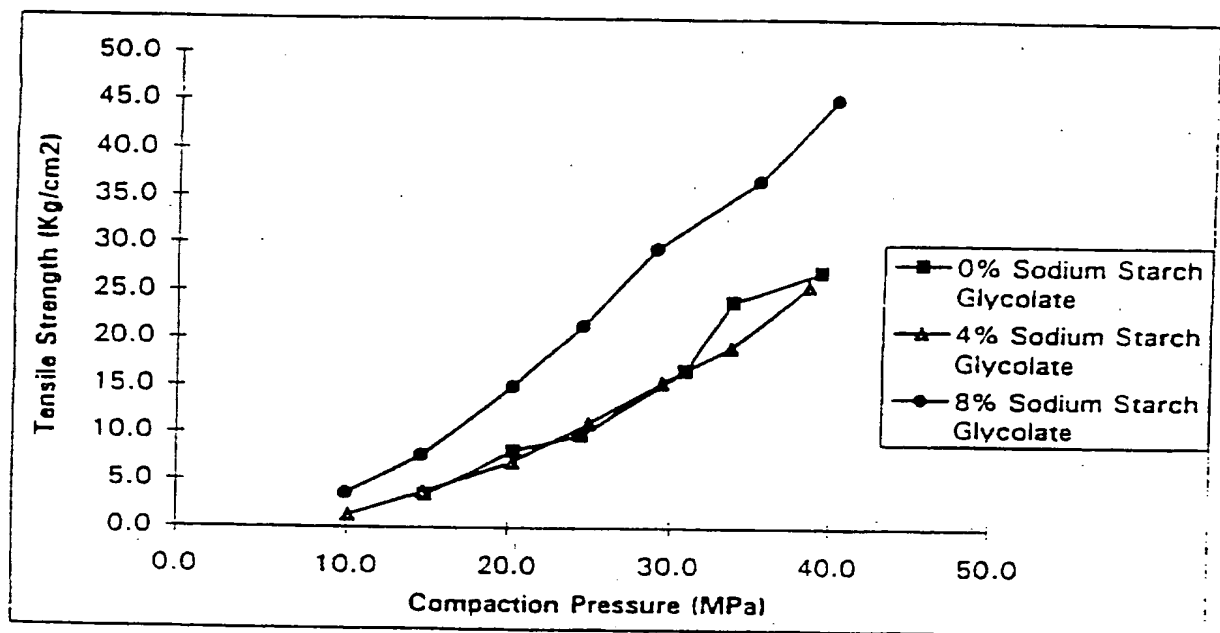
Figure 24

25/55
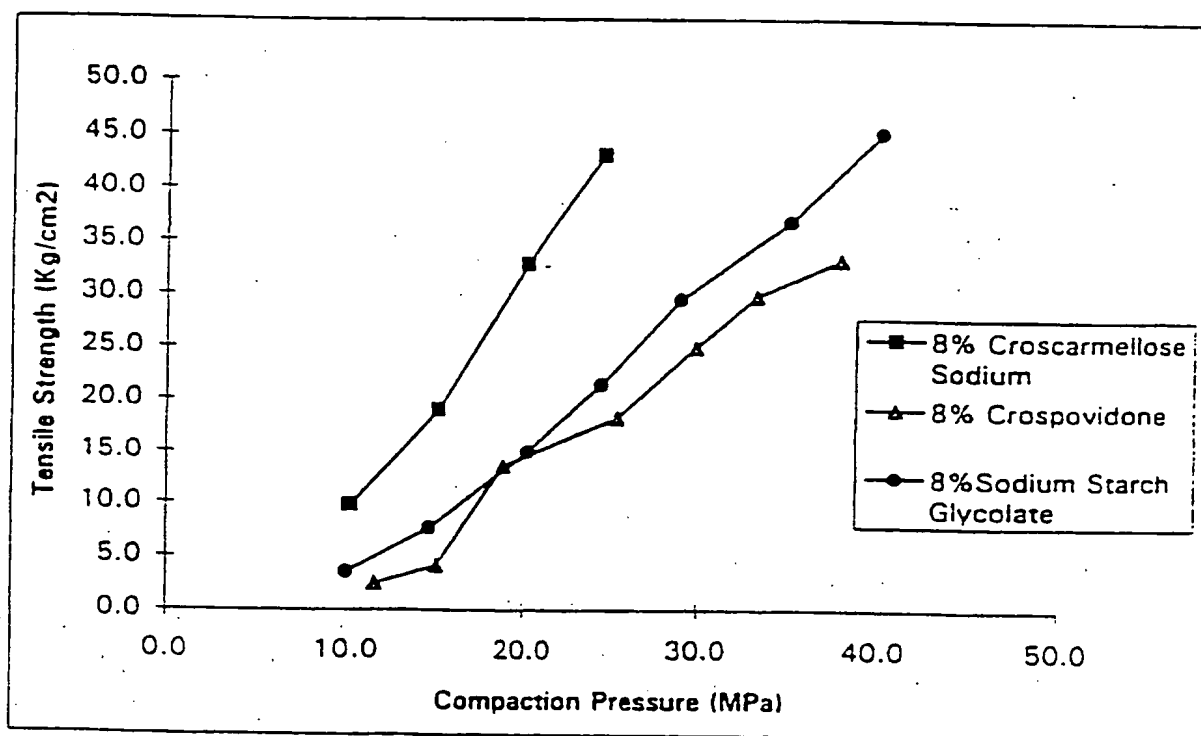
Figure 25

26/55

Figure 26
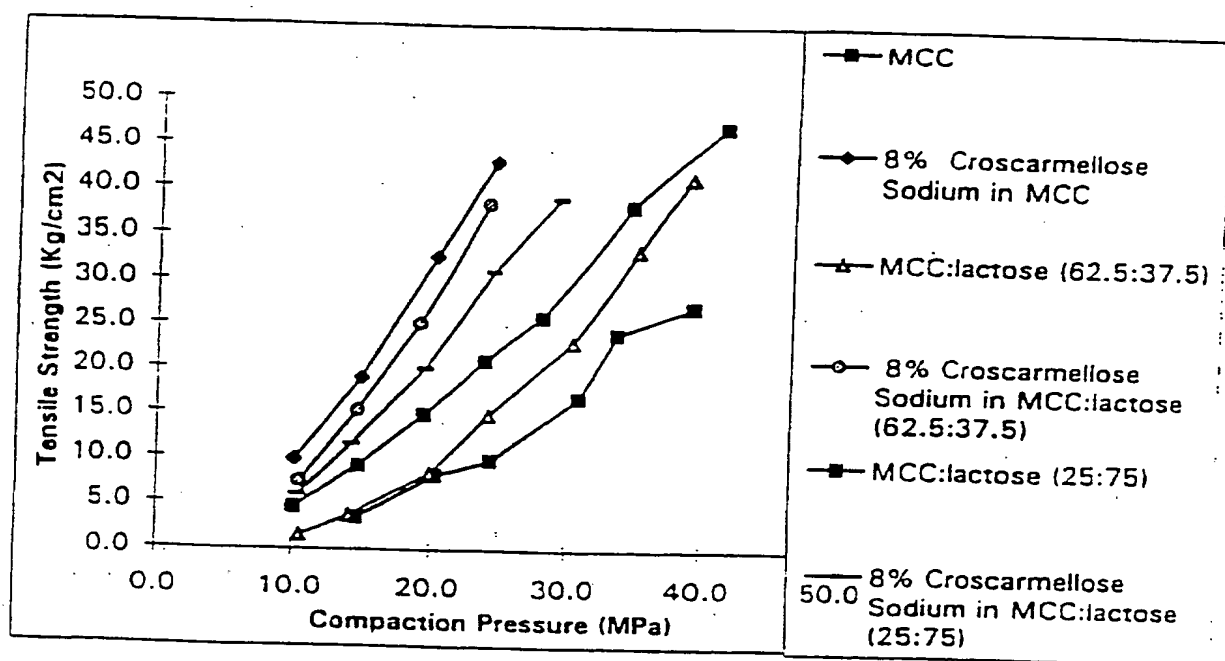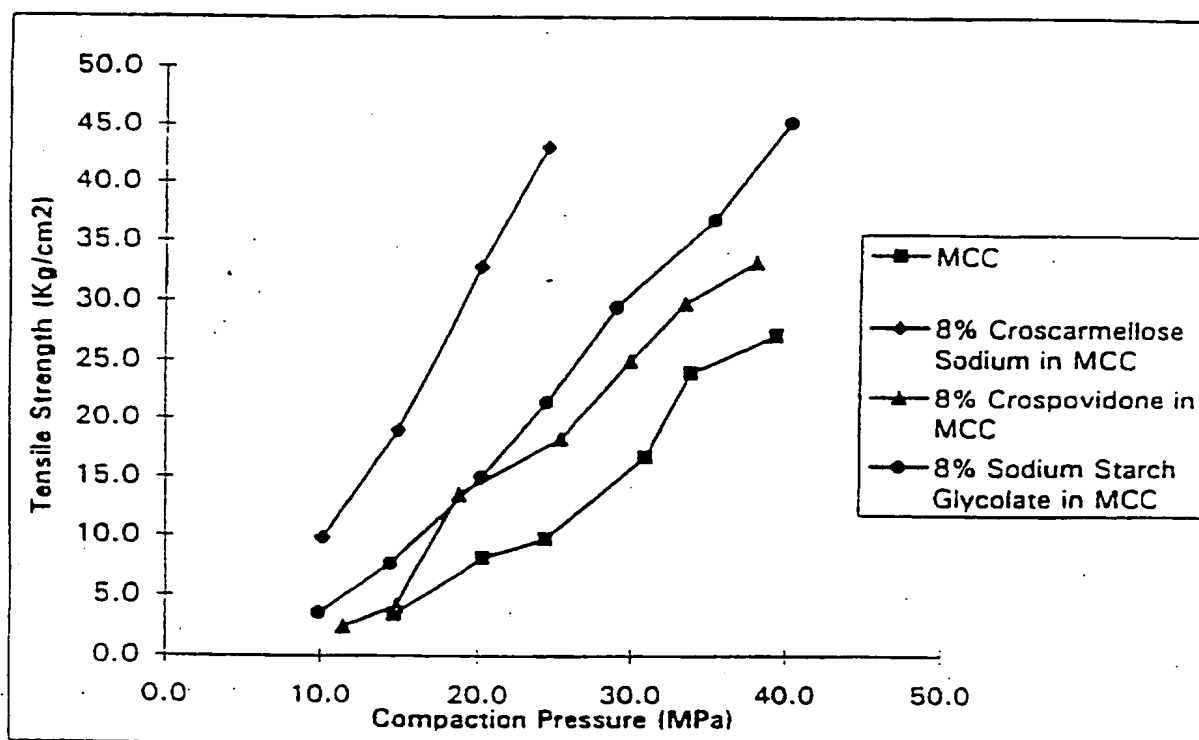
Figure 27

28/55

Figure 28
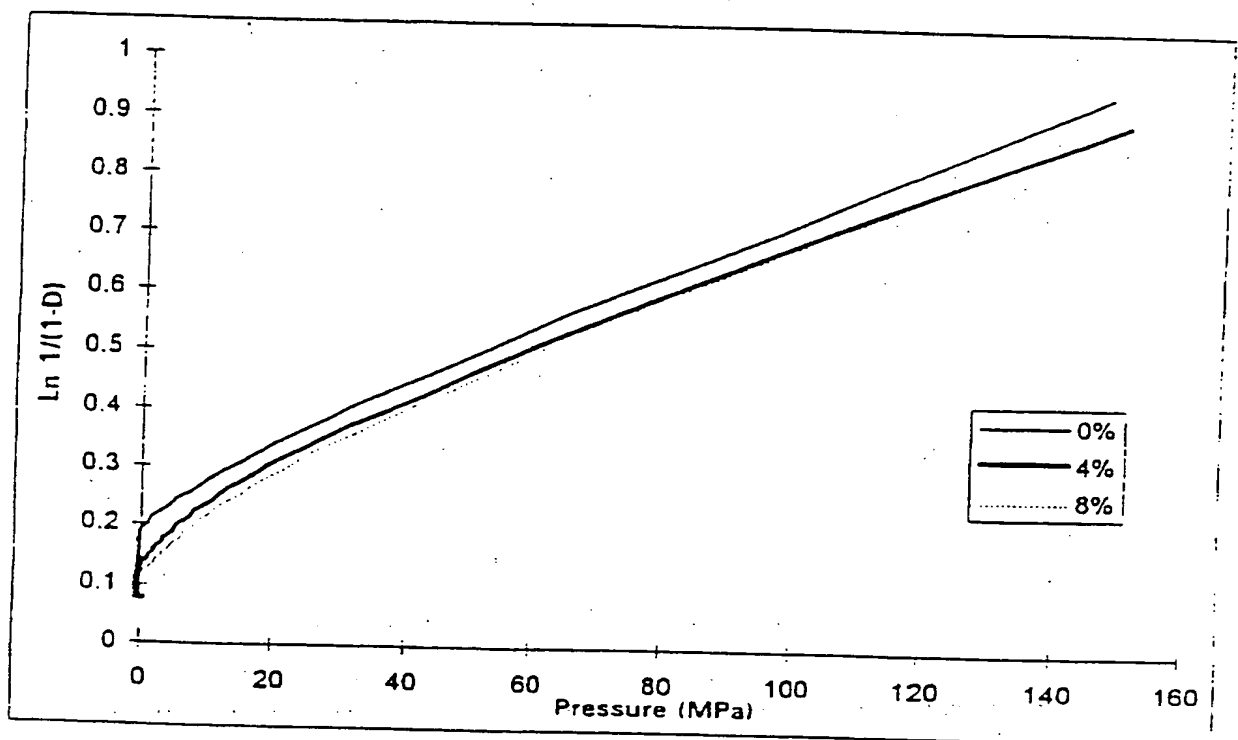
29/55

Figure 29
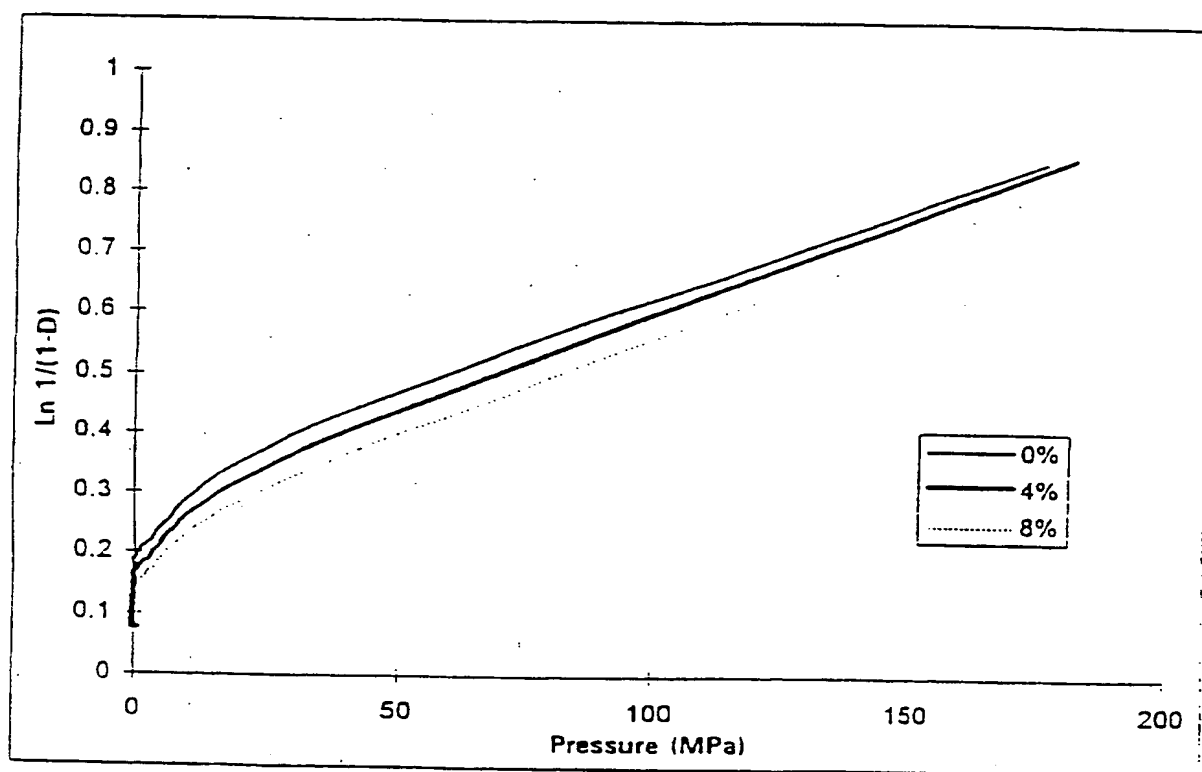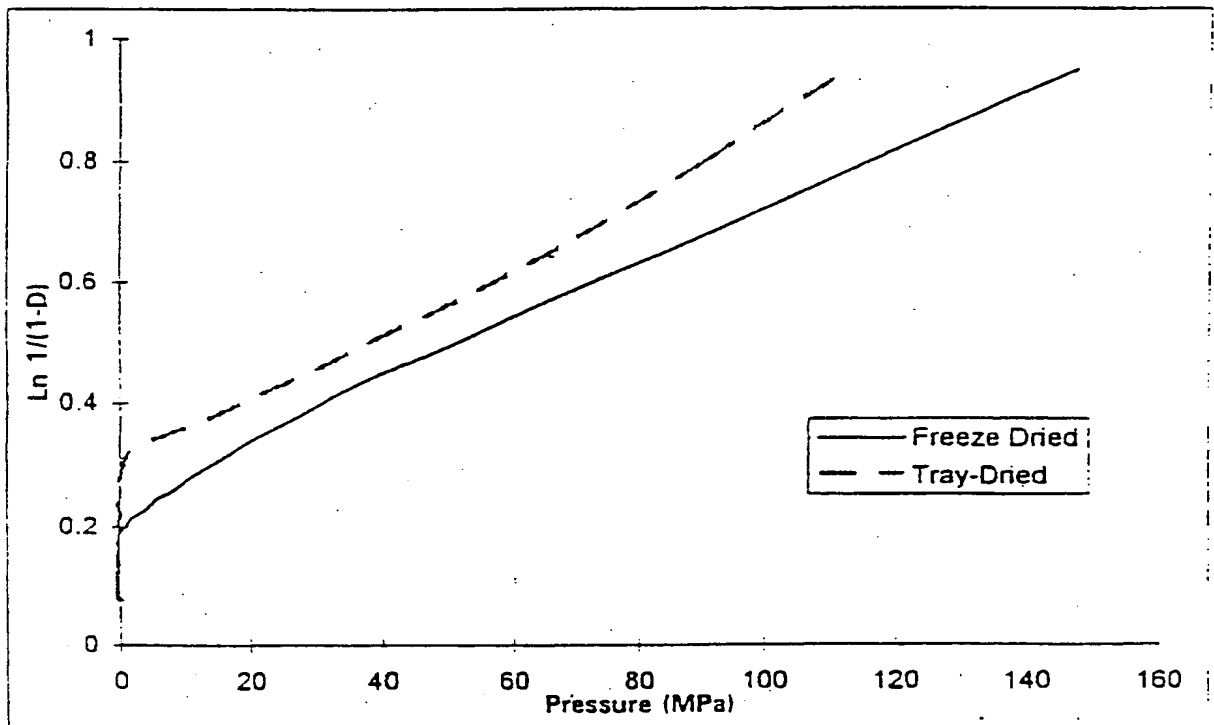
Figure 30

31/55

Figure 31
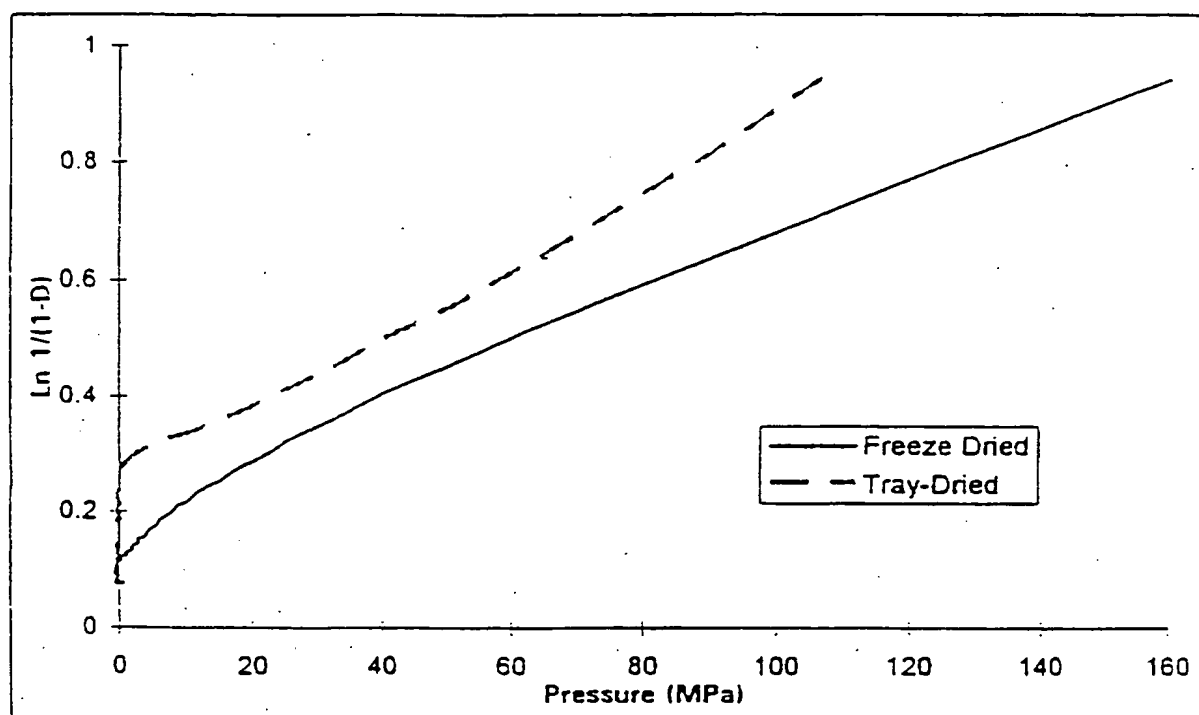
32/55

Figure 32
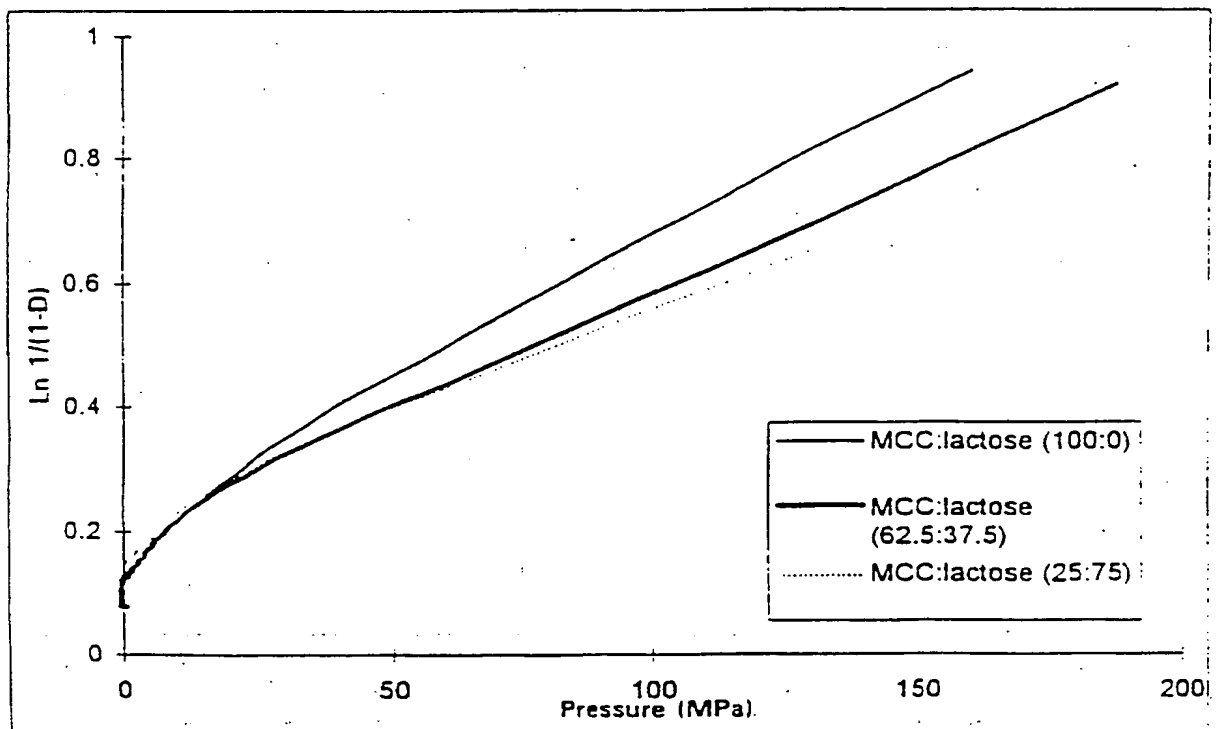
33/55

Figure 33
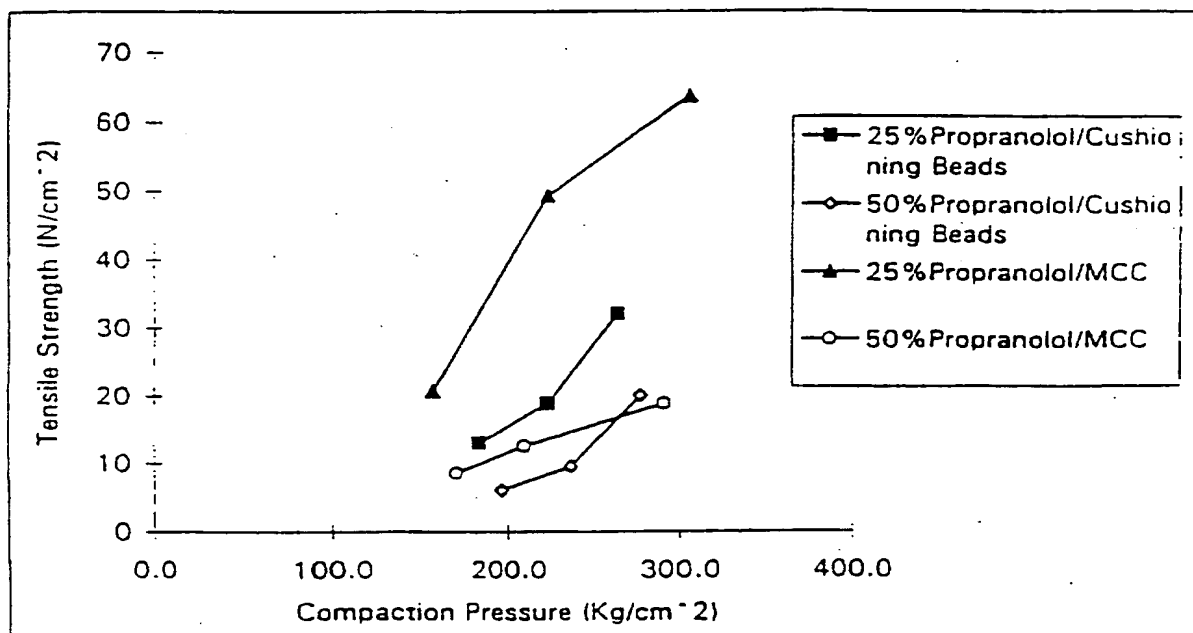
34/55

Figure 34
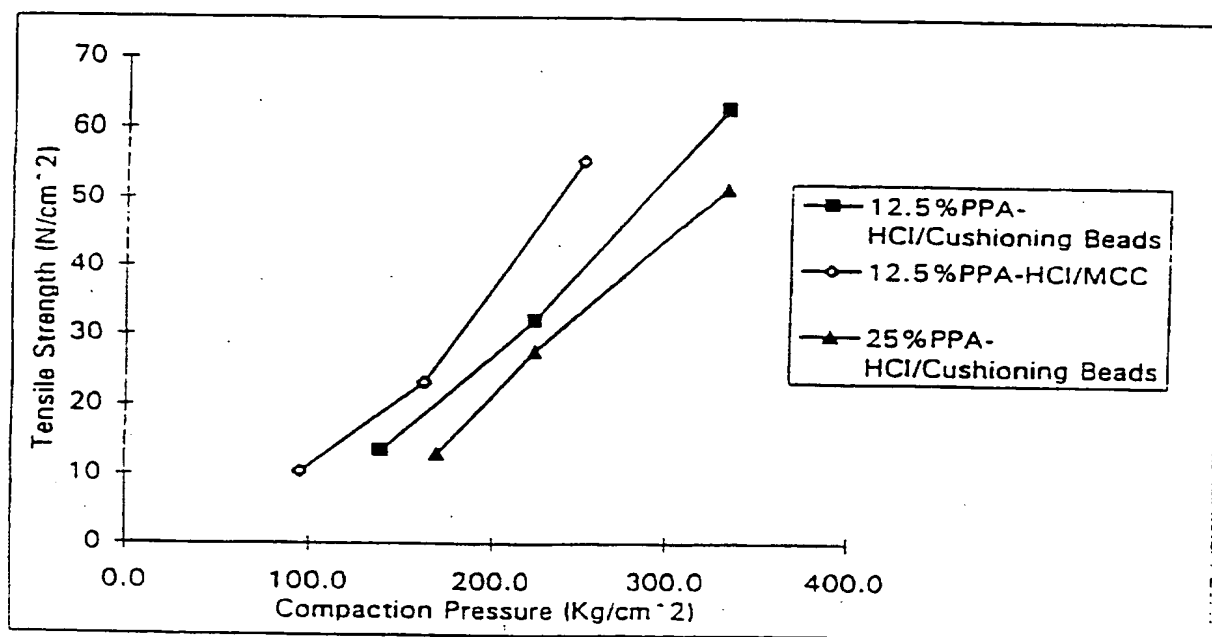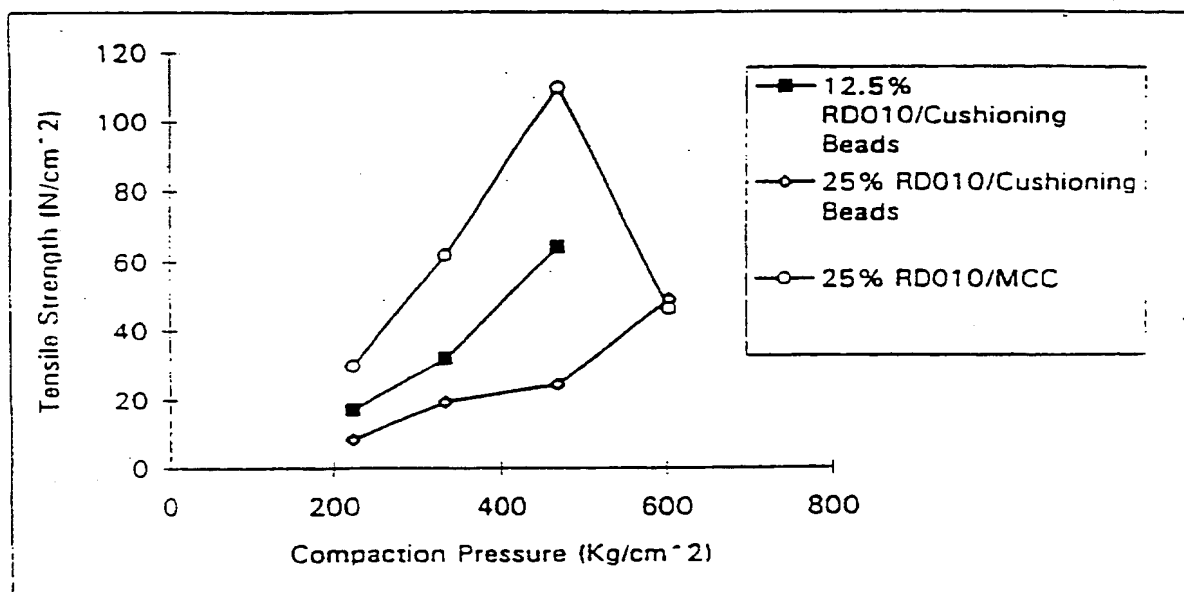
Figure 35

36/55

Figure 36
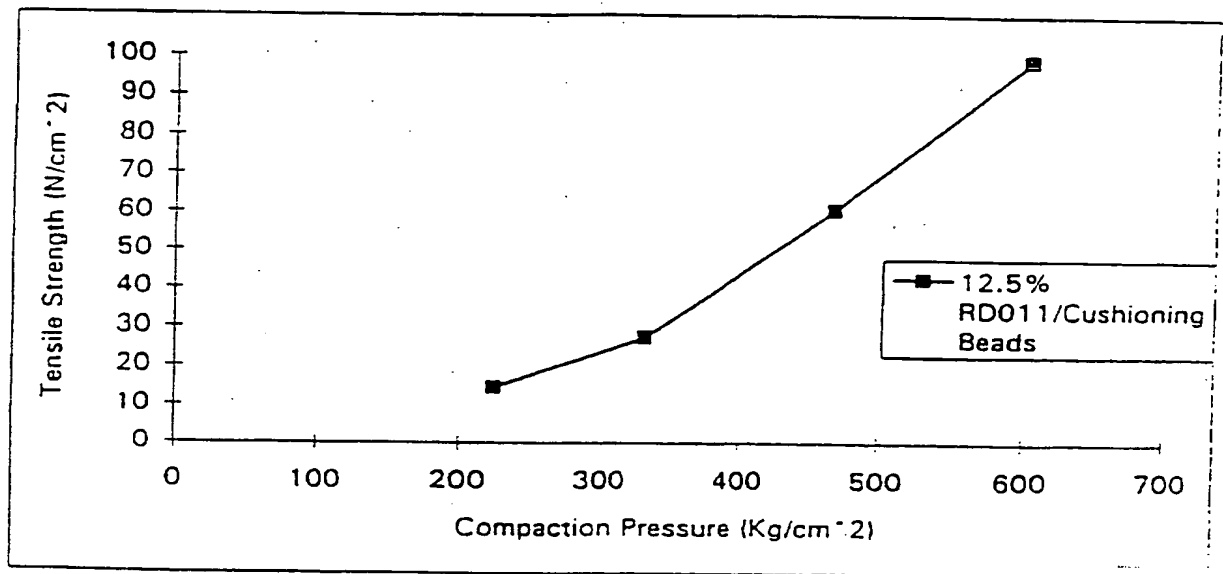
37/55

Figure 37
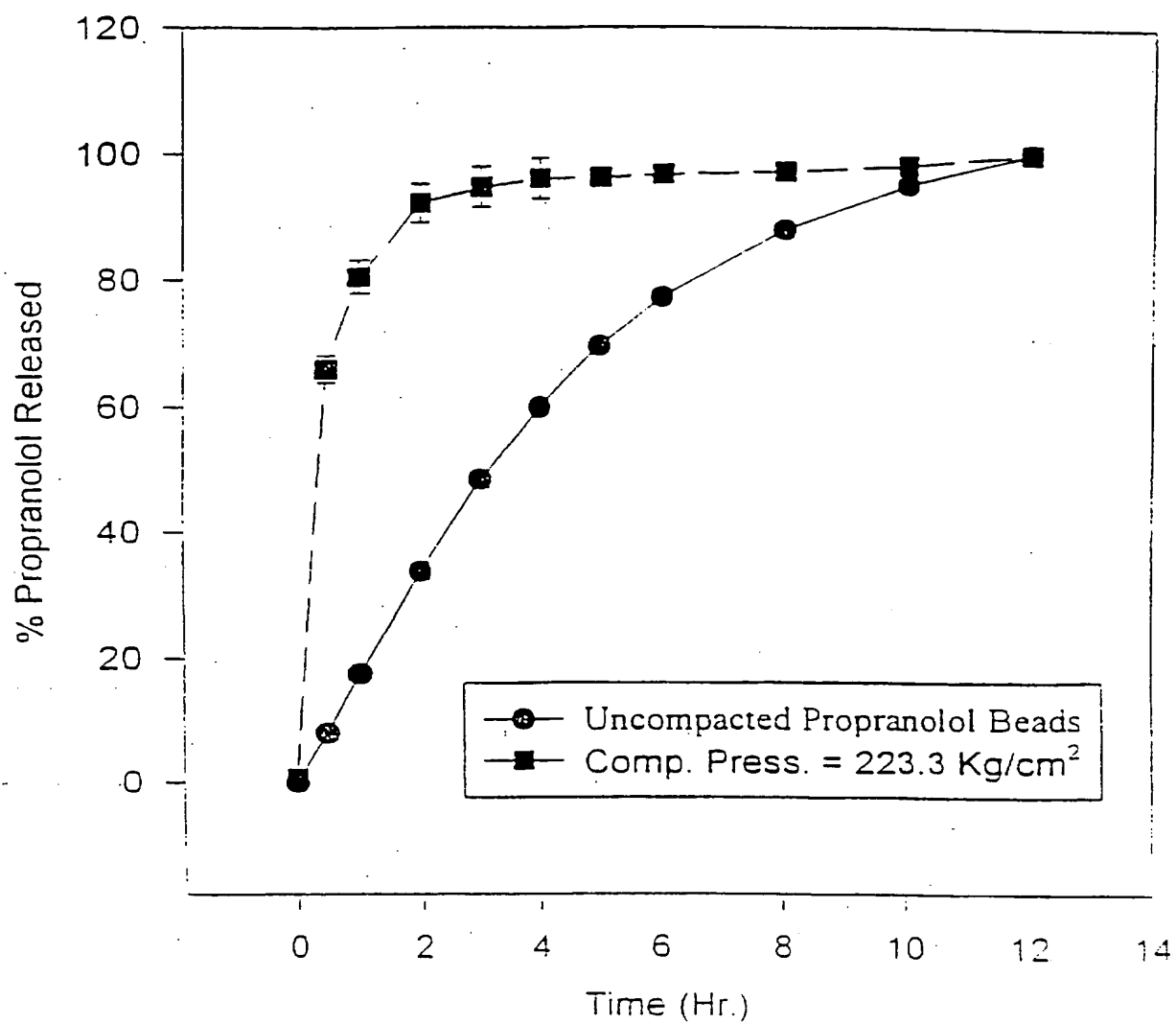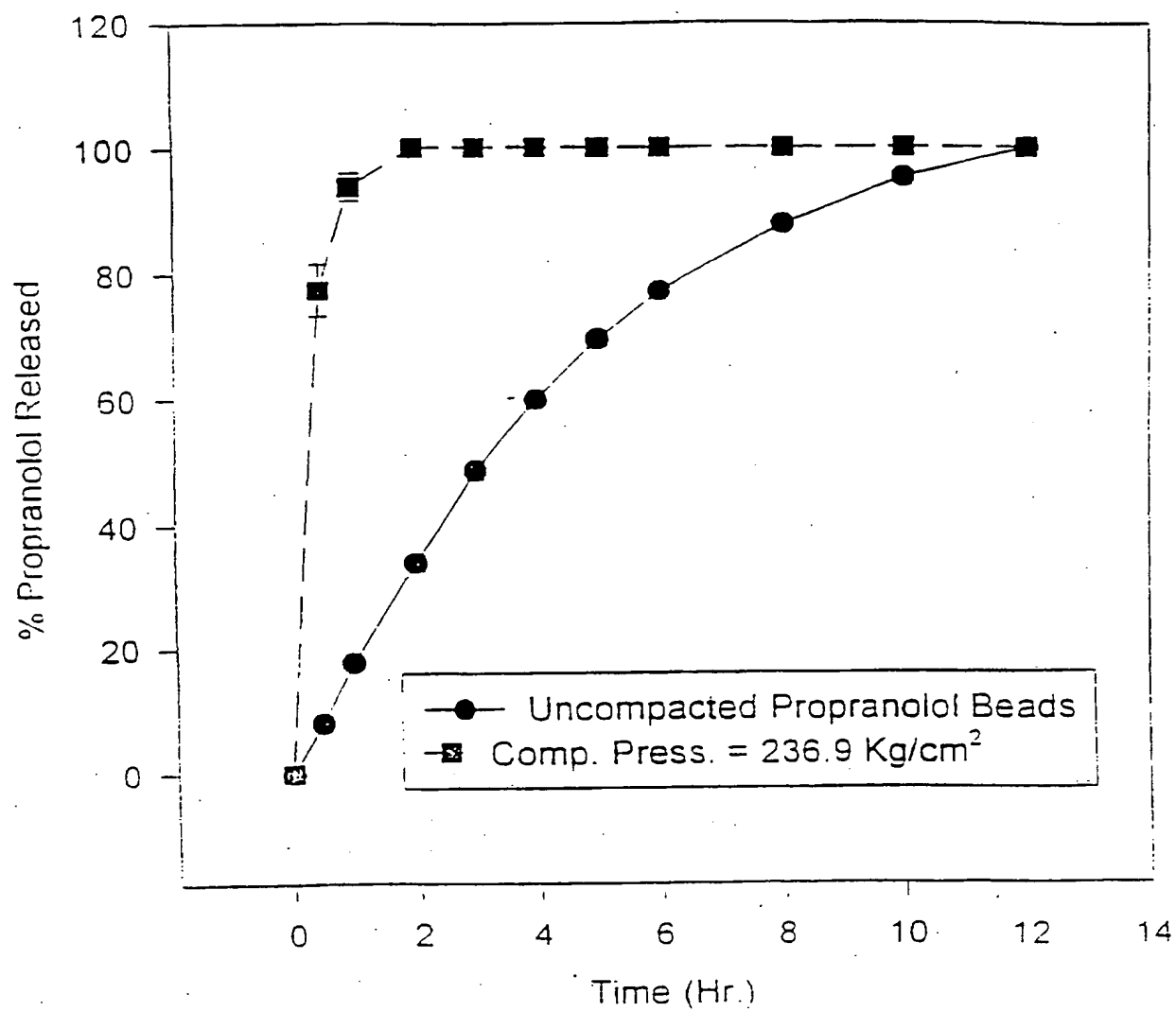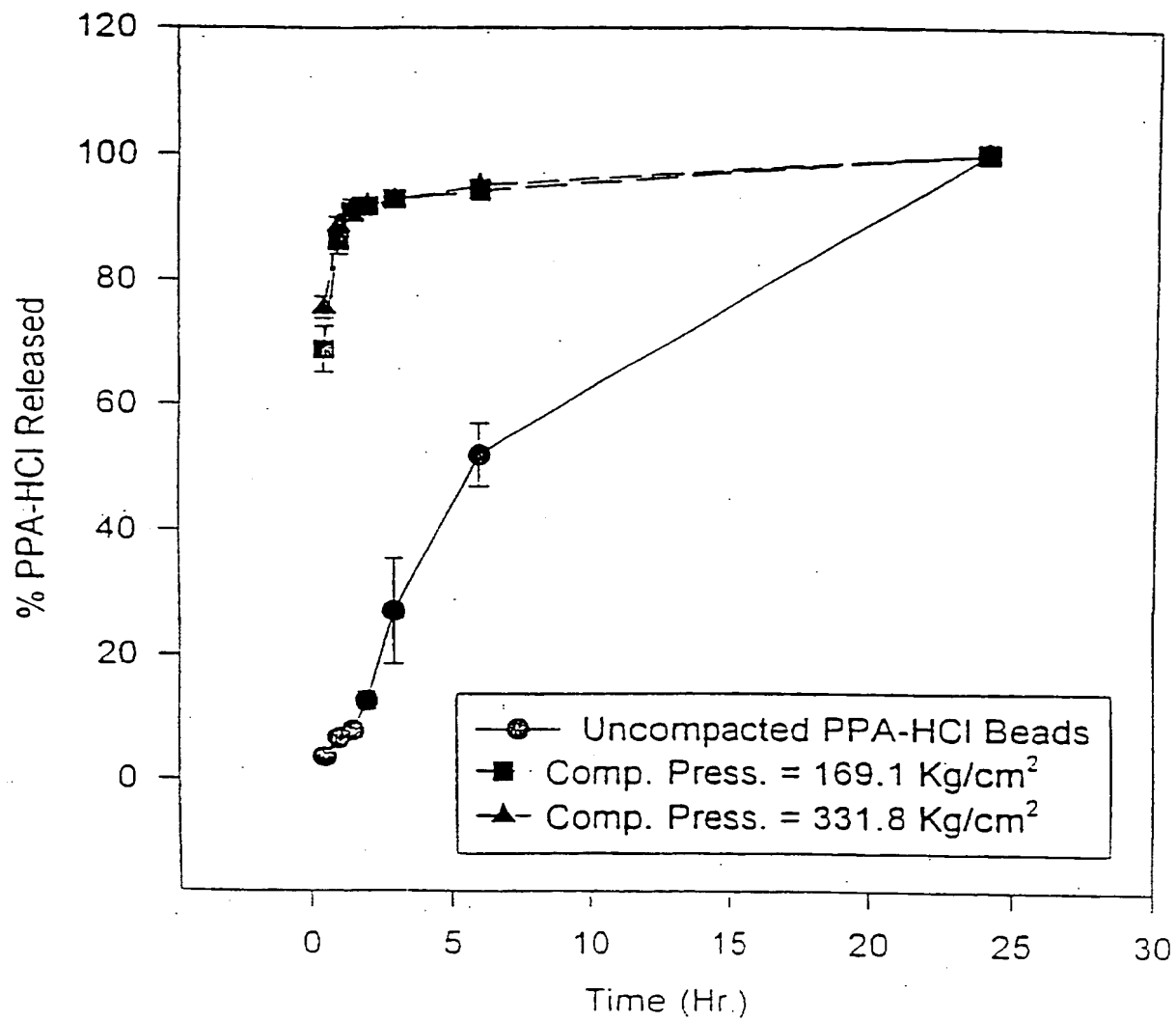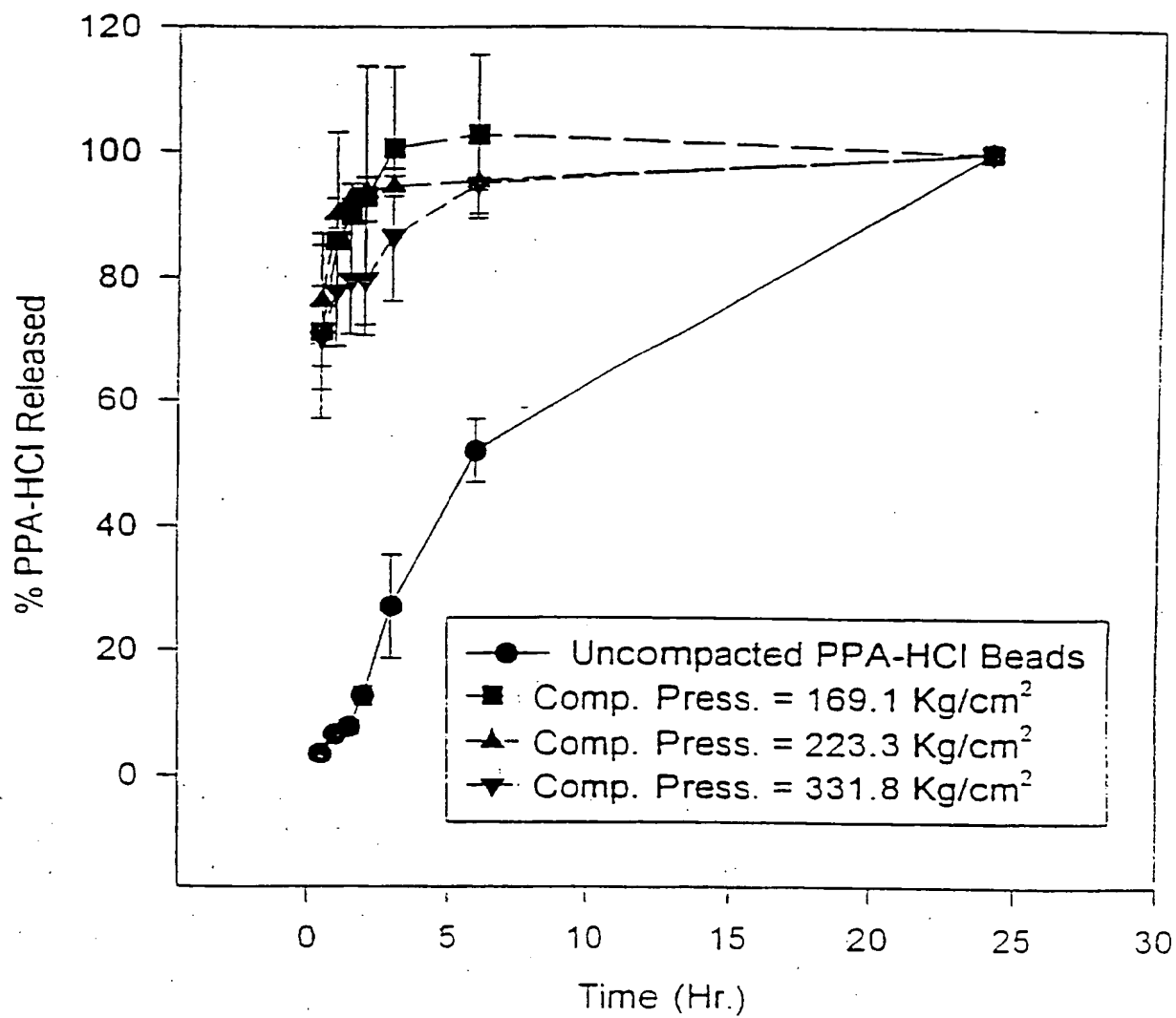
Figure 38

Figure 39

40|55
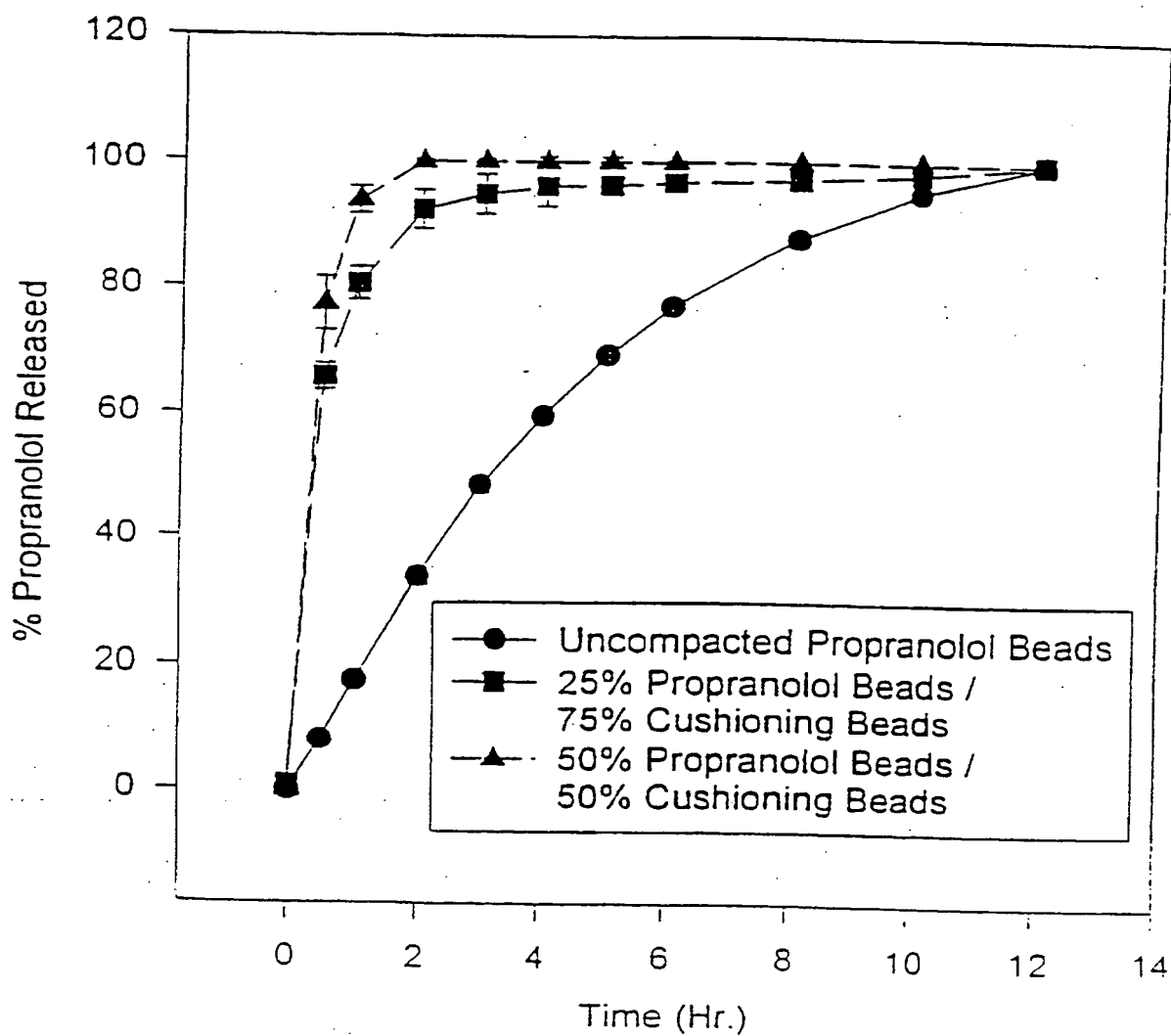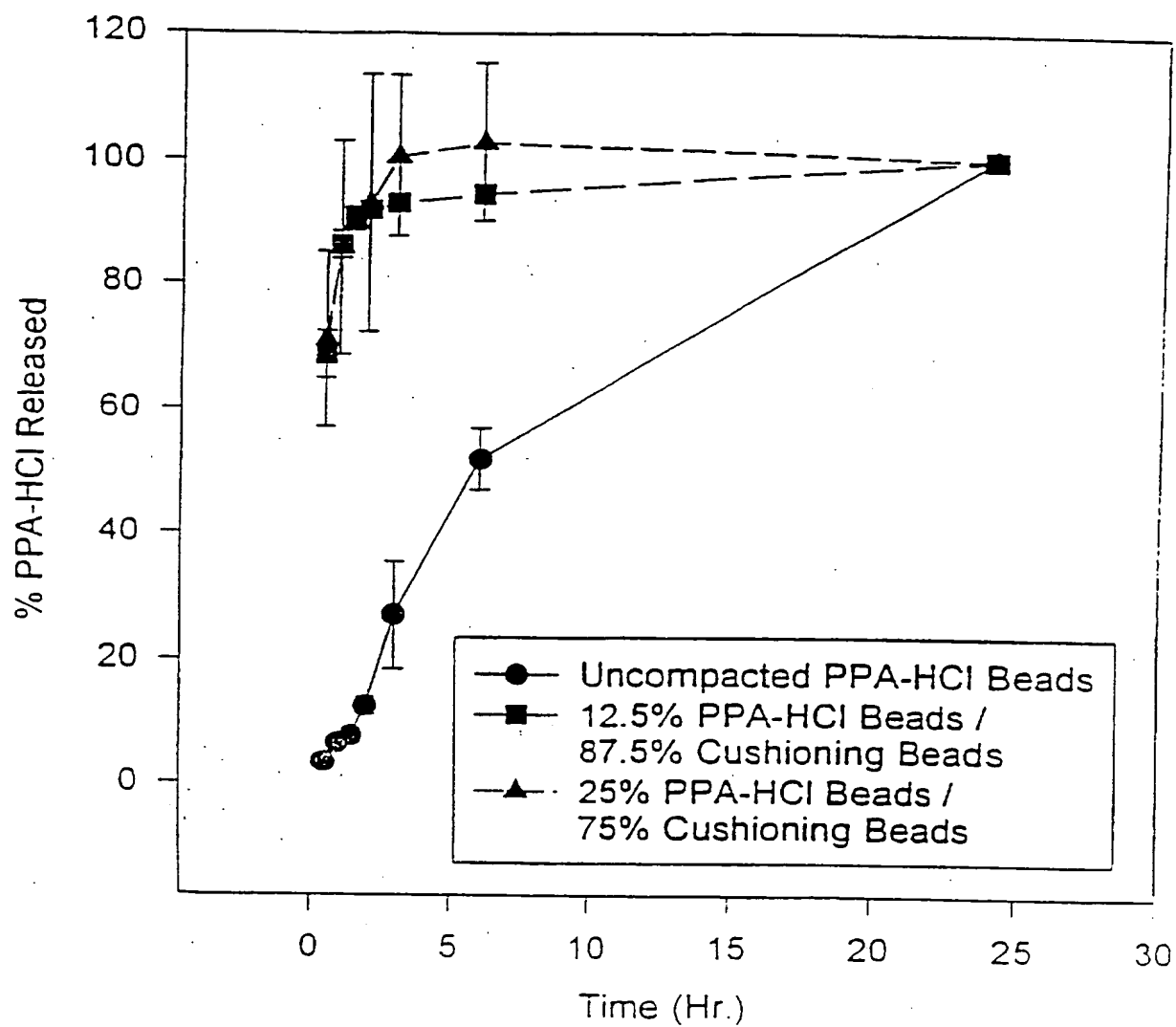
Figure 40
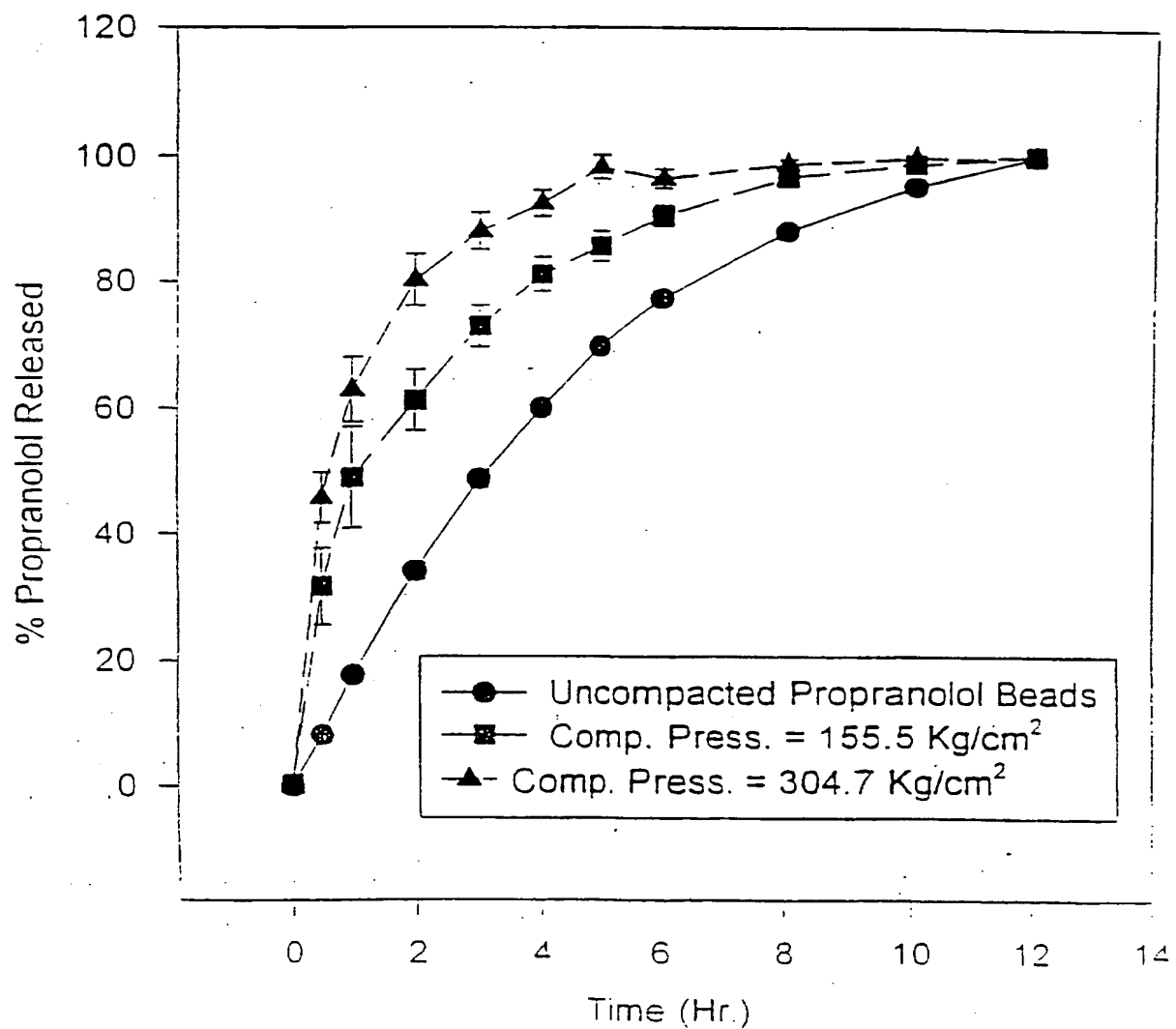
Figure 41
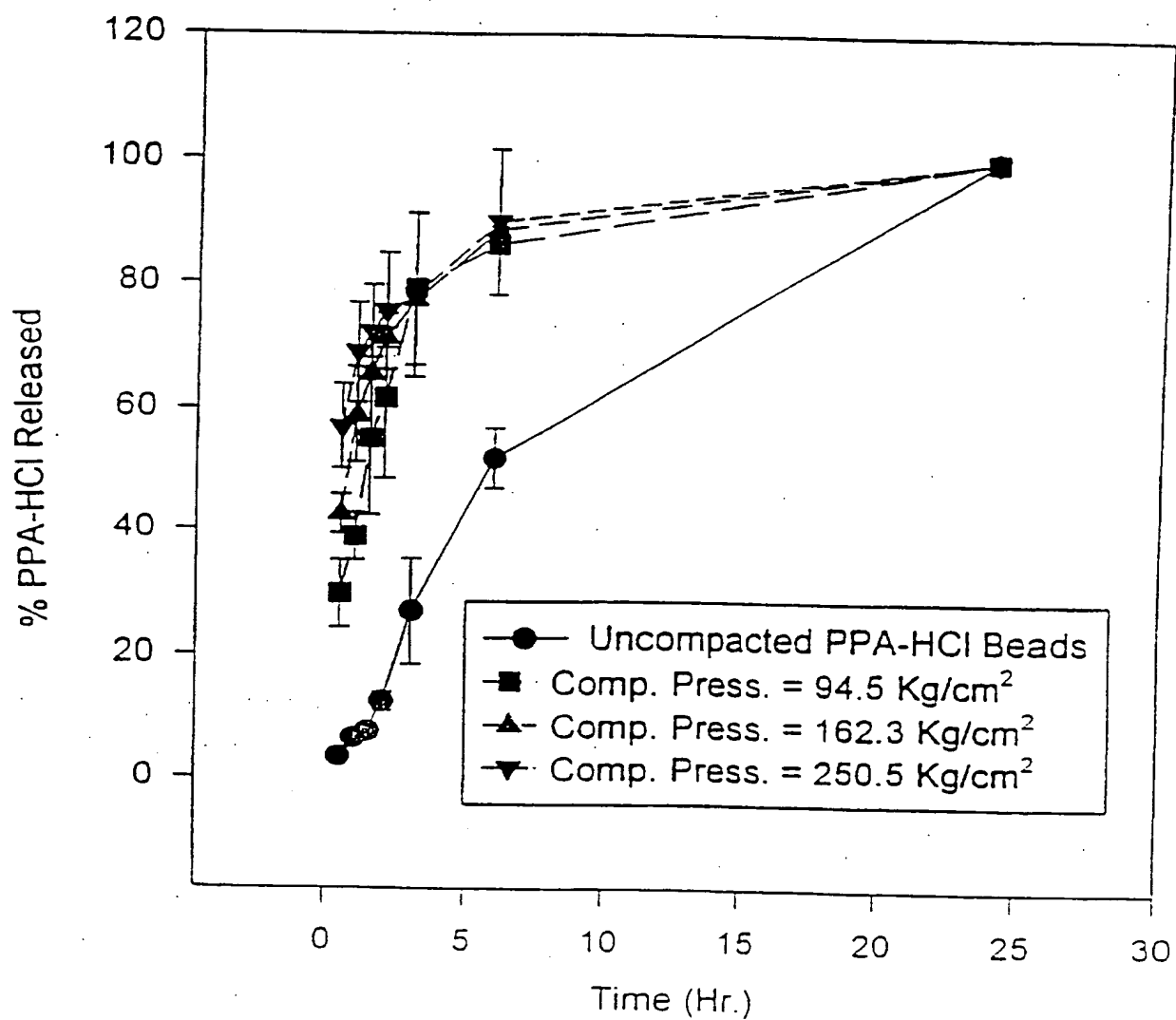
Figure 42

Figure 43

Figure 44

Figure 45

Figure 46

47/55

Figure 47
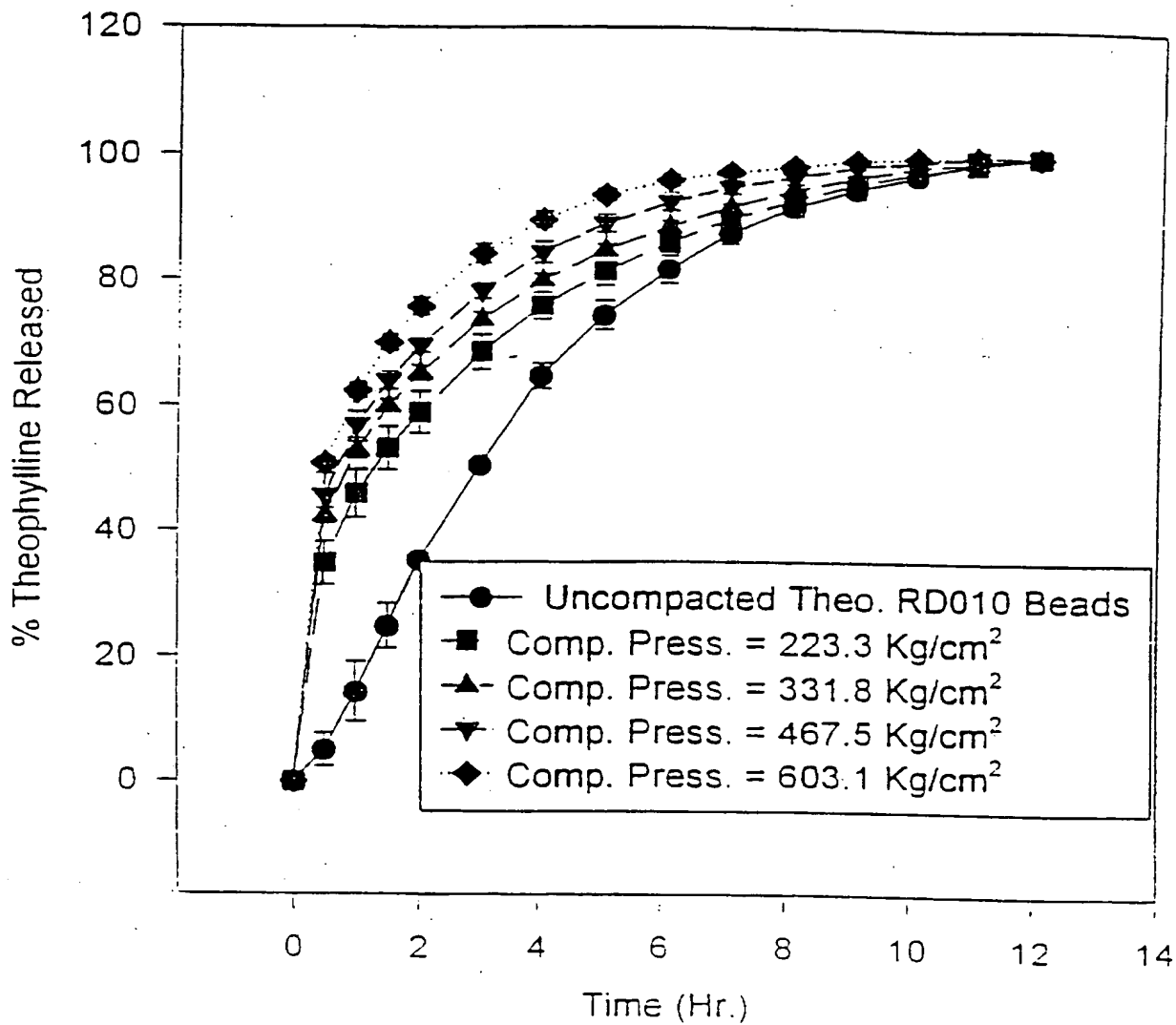
Figure 48

49/55

Figure 49

50/55

Figure 50

Figure 51

Figure 52

Figure 53

Figure 54

Figure 55